

# Use of Mesenchymal Stem Cells (Prochymal™) to Treat Pediatric Patients with Severe (Grade III-IV) acute Graft Versus Host Disease Refractory to Steroid and Other Agents

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Data was presented at the December 2007 American Society of Hematology meeting

## Protocol/Methods

### Background

Severe acute Graft versus Host Disease (aGvHD) that fails to respond to steroids and other immunosuppressive agents is associated with 180 day survival of less than 20%. Preliminary studies have shown that human mesenchymal stem cells (hMSCs, Prochymal™, Osiris Therapeutics, Inc.) have immunomodulatory and tissue regenerative properties. This report summarizes the safety and efficacy of Prochymal for the compassionate treatment of severe (Grades III/IV) acute GvHD in pediatric patients who failed steroids and multiple 2<sup>nd</sup> line immunosuppressive therapies.

### Patients

- 12 pediatric patients with severe aGvHD (Grade III, n=6 and IV, n=6) were treated from July 2005 to July 2007
- To be eligible for compassionate use, patients must have exhausted all reasonable therapeutic alternatives
- Patients had failed an average of 3.2 lines of therapy prior to treatment with Prochymal
- Patients suffered with aGvHD for a median of 30 days (16-181 days) prior to initiation of Prochymal therapy
- Patients from 5 different centers were enrolled
- Median patient age was 6 years (range 0.4-15 years)
- Each treatment plan received IRB and FDA approval

### Prochymal Therapy

#### Treatment Plan:

**Infusion:** Cells were given IV over 1 hour for patients under 35kg and at a rate of 4-6mL/min for patients ≥35kg. Patients received hydrocortisone and diphenhydramine 30 minutes prior to infusion of Prochymal.

**Induction therapy:** 2 x 10<sup>6</sup> MSC/kg/infusion, twice a week for 4 weeks. Patients #s 1 and 2 received 8 x 10<sup>6</sup> MSC/kg/infusion under a different treatment plan (see Table).

**Maintenance therapy:** Option for additional infusions of 2 x 10<sup>6</sup> MSC/kg/infusion, once a week for the subsequent 4 weeks. Therapy was provided to patients who did not achieve a CR during the induction therapy.

#### Prochymal™ (ex vivo cultured human mesenchymal stem cells)

The product was manufactured by Osiris and consists of a population of homogeneous MSCs characterized by cell surface phenotype. hMSCs are isolated from an unrelated, unmatched donor-derived BM aspirate after donor screening and testing according to FDA requirements. The cells are expanded in culture to permit up to 5,000 doses to be obtained from a single donation. The hMSCs are tested for potential pathogens, mycoplasma, sterility, endotoxins and potency. The cells are formulated in Plasmalyte A containing 5% human serum albumin and 10% DMSO and aseptically packaged into Cryocyte bags.

**Preparation.** Cells were thawed and resuspended in Plasmalyte A. The final product had a cell concentration of 2.5 x 10<sup>6</sup> MSC/mL and a DMSO concentration of 3.75%. All products had a cell viability ≥70%. The volume administered was dependent upon body weight.

### Patient Transplantation History

No	Gender	Age	Disease	Conditioning	Stem cells	Donor/match
1	Male	5m	ALD	Red Int	BM+UCB	RD 6/6
2	Male	8m	M Osteopet	Red Int	UCB	UD 4/6
3	Male	6y	HLH	Ablative	BM	UD 10/10
4	Male	2y	Hurler's	Red Int	UCB	UD 4/6
5	Male	13y	APML	Red Int	UCB	UD 4/6
6	Male	2y	AML	Ablative	UCB	UD 5/6
7	Male	15y	HLH	Ablative	UCB+haplo-PBSC	UD 5/6
8	Male	4y	ALL	Ablative	PBSC	UD 9/10
9	Male	15y	AML	Red Int	UCB	UD 5/6
10	Female	2y	MPD/Eos	Ablative	UCB	UD 6/6
11	Female	6y	ANLL	Red Int	UCB	UD 4/6
12	Male	13y	ALL	Ablative	BM	UD 10/10

ALD: adrenoleukodystrophy; HLH: hemophagocytic lymphohistiocytosis; APML: acute promyelocytic leukemia; AML: acute myeloid leukemia; ALL: acute lymphocytic leukemia; MPD/eos: myeloproliferative disease/eosinophilia; ANLL: acute non-lymphocytic leukemia; Hurler's: Hurler's syndrome; M Osteopet: malignant osteopetrosis; Red Int: reduced intensity; BM: bone marrow; UCB: umbilical cord blood cells; PBSC: peripheral blood stem cells; haplo PBSC: CD34 selected cells; RD: related donor; UD: unrelated donor.

### Patient GvHD History

No	Onset aGvHD Post Transplantation	aGvHD Before Prochymal	GvHD Severity at start of Prochymal Infusion	GvHD Therapies prior to Prochymal
	DAYS	DAYS	GRADE	(Number) Agent
1	70	20	IV	(4) Solumedrol, cellcept, infliximab, daclizumab
2	81	45	III	(4) Solumedrol, daclizumab, cellcept, prograf
3	22	46	IV	(3) Solumedrol, infliximab, entanercept
4	98	119	III	(4) Solumedrol, daclizumab, infliximab, budesonide
5	56	181	IV	(2) Solumedrol, daclizumab
6	72	30	IV	(4) Solumedrol, cellcept, infliximab, OKT3
7	27	18	IV	(4) Solumedrol, Zenapax, cellcept, infliximab, rituxan
8	22	76	III	(3) Solumedrol, infliximab, ECP
9	84	19	III	(2) Solumedrol, budesonide
10	33	38	III	(2) Solumedrol, infliximab
11	93	125	III	(3) Solumedrol, daclizumab, cellcept
12	80	157	IV	(3) Solumedrol, daclizumab, cellcept

### GvHD Severity and Prochymal Treatment Plan

No	GI/Skin/Liver (stages)	Grade GvHD	No. Infusions	hMSC/kg /infusion	Treatment Plan
1	4/1/3	IV	21 <sup>a</sup>	8 x 10 <sup>6</sup> ; 2 x 10 <sup>6</sup>	2/wk for 4 wk; 1/wk 13 wk
2	3/3/0	III	2	8 x 10 <sup>6</sup>	Day 1 & 4
3	4/2/0	IV	12	2 x 10 <sup>6</sup>	2/wk for 4 wk; 1/wk for 4 wk
4	3/0/0	III	12	2 x 10 <sup>6</sup>	2/wk for 4 wk; 1/wk for 4 wk
5	4/0/2	IV	9	2 x 10 <sup>6</sup>	2/wk for 4 wk; 1/wk for 4 wk
6	4/0/0	IV	8	2 x 10 <sup>6</sup>	2/wk for 4 wk
7	4/1/3	IV	12	2 x 10 <sup>6</sup>	2/wk for 4 wk; 1/wk for 4 wk
8	4/1/0	IV	7	2 x 10 <sup>6</sup>	2/wk for 4 wk
9	3/0/0	III	8	2 x 10 <sup>6</sup>	2/wk for 4 wk
10	3/0/0	III	3 <sup>b</sup>	2 x 10 <sup>6</sup>	2/wk for 4 wk
11	3/0/0	III	8	2 x 10 <sup>6</sup>	2/wk for 4 wk
12	4/0/1	IV	12+8 <sup>c</sup>	2 x 10 <sup>6</sup>	2/wk for 4 wk; 1/wk for 4 wk; 2/wk for 4 wk

<sup>a</sup> 11 infusions were administered at 8 x 10<sup>6</sup> hMSC/kg and 10 infusions were administered at 2 x 10<sup>6</sup> hMSC/kg  
<sup>b</sup> Patient was discontinued at parents' request  
<sup>c</sup> Patient was continued on therapy to allow for removal of steroids

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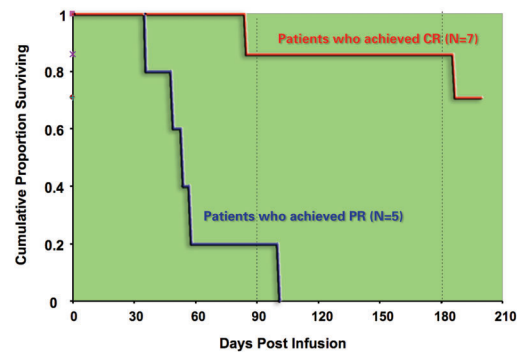
## Results

### GvHD Response

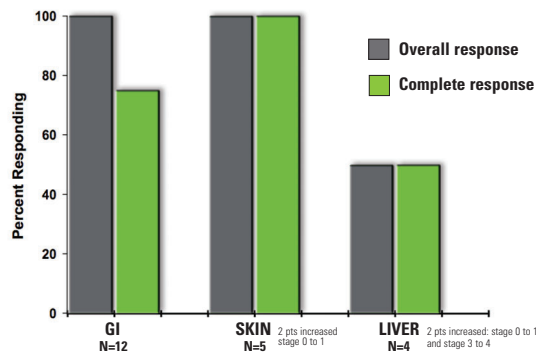
All patients responded to Prochymal therapy; 7 (58%) patients achieved a CR

No	Prior to Prochymal Treatment		After Completion of Prochymal Treatment		Response
	GI/Skin/Liver (stages)	Grade	GI/Skin/Liver (stages)	Grade	
1	4/1/3	IV	0/0/4	IV	PR
2	3/3/0	III	0/0/0	0	CR
3	4/2/0	IV	0/0/0	0	CR
4	3/0/0	III	0/0/0	0	CR
5	4/0/2	IV	3/1/2	III	PR
6	4/0/0	IV	0/0/0	0	CR
7	4/1/3	IV	0/0/0	0	CR
8	4/1/0	IV	0/0/0	0	CR
9	3/0/0	III	1/0/0	I	PR
10	3/0/0	III	2/0/0	II	PR
11	3/0/0	III	0/1/1	II	PR
12	4/0/1	IV	0/0/0	0	CR

### Survival and Response



### Response by Organ System



### Current Status

- All patients tolerated treatment and there were no SAEs related to the administration of Prochymal
- 100 day survival (from initiation of Prochymal) is 58% (7/12)
- By publication (median follow up 229 days), 7 patients had died
- Patient survival and response status

Part #	Death post 1st infusion DAY	Response	Cause
7*	85	CR	Multiorgan failure, fungal infection
3	185	CR	Sepsis
5	36	PR	CMV encephalitis
11	49	PR	Respiratory failure, fungal infection
10	54	PR	EBV LPD
9	58	PR	Multiorgan failure, EBV LPD
1	101	PR	Sepsis, candida

\* Patient received a liver transplantation for severe hepatitis on day 19 after starting induction therapy.

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## Summary/Conclusion

### Summary

- **All patients achieved a clinical response in at least one organ system after Prochymal infusions**
- **58% (7/12) of the patients achieved a complete response at the end of Prochymal therapy**
- **Best responses were seen in patients with severe (stages 3/4) GI GvHD:**
  - 75% (9/12) achieved a complete resolution of GI symptoms
- **42% (5/12) of the patients are alive with a median follow up of 229 days**
- **All surviving patients had achieved a complete response**
- **The infusion of Prochymal was safe and well tolerated. No infusional toxicities were observed**

### Conclusions

- **The administration of Prochymal to patients who had failed steroids and multiple other therapies for their severe acute GvHD resulted in significant clinical responses and survival**
- **Prochymal represents a very promising new treatment option**
- **Phase III placebo-controlled clinical trials are underway**