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Placenta-derived mesenchymal-like cells (PDA-001) as therapy for chronic pulmonary sarcoidosis: a phase 1 study

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Abstract. *Background*: Placental derived mesenchymal-like cells have been found to have immunosuppressive effects on T cell function. We studied mesenchymal-like cells as immunomodulators in chronic pulmonary sarcoidosis. *Methods*: PDA-001 cells were culture-expanded in vitro as a plastic-adherent, undifferentiated cell population that expresses the nominal phenotype CD34-, CD10+, CD105+ and CD200+. Four patients with refractory pulmonary sarcoidosis received two infusions of 150 million PDA-001 cells in 240 ml dextran-40 solution one week apart. During and for two hours after the first infusion, the pulmonary artery pressure was monitored. Prior to first infusion and within 24 hours after the second infusion, bronchoscopy and bronchoalveolar lavage (BAL) were performed. Patients underwent initial and serial pulmonary function testing and were followed for two years. *Results*: After the first infusion, all patients had a mild, non-clinically significant increase in mean pulmonary artery pressure, but none exhibited right heart failure or volume overload. In the year following treatment, there was no significant change in the FVC, but two patients had improvement in their chest x-ray and had prednisone withdrawn. BAL samples after the second infusion were sufficiently viable to undergo FACS analysis in three cases and in two patients, CD10+CD49c+C105+ cells (indicative of PDA-001 cells) were found. *Conclusion*: The use of placental derived mesenchymal-like cells led to a mild increase in pulmonary artery pressure. In some cases, these cells were found in the BAL 24 hours after the second dose. Two of four patients demonstrated some steroid sparing benefit, including one patient with prolonged remission. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 106-114)*

Key words: stem cells, pulmonary artery pressure, bronchoalveolar lavage, pulmonary sarcoidosis

Introduction

A significant proportion of sarcoidosis patients require chronic therapy (1). For this group of patients, several drugs have been proposed as alternatives to glucocorticoids. These alternatives include steroid sparing agents such as methotrexate, azathioprine, and leflunomide (2). For patients who have progressive disease despite aggressive conventional immunosuppression, biological agents such as infliximab, adalimumab, and rituximab have been reported as effective in some cases (3-5). However, these biologic agents have significant toxicities and are not successful in treating all cases. PDA-001(cenplacel-L) is a mesenchymal-like cell population derived

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from normal, full-term human placental tissue. PDA-001 cells are culture-expanded *in vitro* as a plastic-adherent, undifferentiated cell population that expresses the nominal phenotype CD34-, CD10+, CD105+ and CD200+. PDA-001 cells constitutively express moderate levels of HLA Class I and undetectable levels of HLA Class II (6). Mesenchymal stromal cells (MSCs) and MSC-like cells derived from human placenta have been found to have immunosuppressive effects on T cell function (7, 8). The T cell immunosuppression may be enhanced by gamma interferon (9), a key cytokine in the granulomatous response of sarcoidosis (10). PDA-001 is of potential therapeutic utility for a variety of immune and inflammatory diseases and is in clinical trials for the treatment of Crohn's disease (11). Based on its mechanism of action, cell therapy with placenta-derived MSCs or MSC-like cells such as PDA-001 may represent a novel treatment of chronic pulmonary sarcoidosis.

Pulmonary vascular disease is common in advanced pulmonary sarcoidosis. In one study of persistently dyspneic sarcoidosis patients, half were found to have pulmonary hypertension (12). Since mesenchymal-like cells are known to be retained in the lung when administered intravenously, it is essential to determine the acute effect of cell therapy on the pulmonary artery pressure in this patient population. We therefore performed a Phase I trial of PDA-001 in patients with advanced pulmonary sarcoidosis in which we monitored pulmonary artery pressure during the infusion of the cells.

Methods

Patient selection

Patients with advanced pulmonary sarcoidosis were recruited from those seen at two sarcoidosis clinics in the United States (University of Cincinnati and Cleveland Clinic). Patients diagnosed with sarcoidosis based on standard criteria (13) were eligible for the study. Patients had parenchymal disease on chest radiograph (Stage II or III) with disease duration of more than one year. Patients had to have a forced vital capacity of ≥ 45% and ≤ 80% of predicted normal value at screening and were on a stable dose of prednisone, methotrexate, azathioprine, and/or leflunomide for 4 weeks prior to first treatment. Patients were excluded if they had clinically apparent cardiac or neurosarcoidosis, history of pulmonary embolism or deep vein thrombosis, were active or previous smokers of greater than 10 pack years, morbidly obese, received prior anti-tumor necrosis factor monoclonal or B cell depleting antibodies, had active infection in thirty days prior to first treatment, prior infection with tuberculosis, HIV, or hepatitis B or C, or clinically significant liver or renal dysfunction. All patients provided written informed consent of a protocol approved by the each Institutional Review Board. The protocol was registered at ClinicalTrials.gov as NCT01440192.

Study Procedures

One to four weeks prior to the first infusion, patients underwent bronchoscopy with bronchoalveolar lavage (BAL). Lavage was performed in a non-dependent lobe, usually the right middle lobe, using a standard protocol (14). A total of 120-240 ml of saline was instilled using sixty ml aliquots and aspirated by hand held syringe. An aliquot of fluid was used to determine cell and differential count. The remaining fluid was sent for detailed analysis of cell population.

Cryopreserved PDA-001 cells were shipped to the study site and stored at < -120°C. Immediately prior to infusion, PDA-001 cells were thawed, diluted with infusion grade dextran 40 and transferred to an infusion bag through the port(s) of the bags using sterile technique. Prior to infusion, subjects were pre-dosed with 50 mg diphenhydramine IV and 50 mg hydrocortisone IV. For all subjects, PDA-001 cells were given as one infusion of the thawed cells mixed with sufficient diluent (infusion grade dextran 40) to achieve a total volume of 240 ml per infusion, within 4 hours of thaw time.

Each subject received 2 infusions of 150 million PDA-001 cells one week apart. The infusion occurred over 120 minutes via a 20-22 gauge catheter inserted into a peripheral arm vein. Immediately following completion of each infusion, the IV line was flushed with 50-100 mL of normal saline.

The study consisted of 3 phases: pre-treatment phase in which subjects were screened for study eligibility; treatment phase in which subjects were to receive PDA-001 infusions on Day 0 and Day 7; and

a follow-up phase in which subjects were evaluated on Study Day 15 (one week after final cell infusion), Study Day 22 (two weeks after final cell infusion), Study Day 29 (three weeks after final cell infusion), Study Day 36 (four weeks after final cell infusion), Study Day 180 (6 months after final cell infusion) and 12, 18 and 24 months post-dosing. At each of the visits, venous blood was sampled for measurement of complete blood count, serum renal and hepatic function and serum biomarkers of disease.

A pulmonary artery catheter was placed prior to the first dose to monitor hemodynamic pressures during the infusion and for 2 hours after completion of the infusion. The infusion was to be stopped if the patient had an increase of mean PA pressure of 10 mm Hg from baseline. In addition, subjects were monitored for heart rate, respiration, blood pressure, body temperature and blood oxygen saturation every 15 minutes throughout the infusion and every 15 minutes throughout the 2-hour post-infusion monitoring period. Subjects were hospitalized overnight for observation after completion of the post-infusion monitoring period and removal of the pulmonary artery catheter.

The second dose of PDA-001 was administered on Study Day 7. Subjects were again pre-dosed with 50 mg diphenhydramine and 50 mg hydrocortisone intravenously 15-30 minutes prior to the start of the infusion. Subjects were monitored for heart rate, respiration, blood pressure, body temperature, and blood oxygen saturation every 15 minutes throughout the infusion and every 15 minutes throughout the 2-hour post-infusion monitoring period.

The next morning, patients returned to undergo bronchoscopy with bronchoalveolar lavage in the same area as the pre-infusion bronchoscopy. Again 120-240 ml of saline was instilled and aspirated by hand held syringe. An aliquot of fluid was used to determine cell count and differential. The remaining fluid was sent for detailed analysis of cell population.

Patients were seen 15, 29, 57, 85, 169, 366, 548, and 731 days after initial dosing and underwent repeat pulmonary function testing at each visit. In addition, CT scans of the chest, abdomen, and pelvis were performed initially and at months 6, 12, 18, and 24 to evaluate for recurrence of disease or development of lymphoproliferative lesions.

Bronchoalveolar lavage (BAL) fluid specimens were shipped to a central laboratory and were received in Cyto-Chex BCT (Streck Labs, USA) on ice and prepared for flow cytometric analysis. Samples containing red blood cells were lysed with 1 part Ammonium Chloride (Stem Cell Technologies, Canada) to 3 parts BAL fluid for 10 minutes on ice. Lysed samples were centrifuged for 5 minutes, 4°C, 400g. Supernatants were decanted and pellet washed with 20 ml of 1X D-PBS (Invitrogen, USA) and 5% Fetal Bovine Serum (Invitrogen, USA). After decant, cells were resuspended in PBS/FBS and counted. Multiple aliquots of samples were prepared at a concentration of $1x10^6$ cells/ml and transferred to 12x75PP tubes (BD Bioscience, USA). An aliquot of frozen PDA-001 cells was rapidly thawed in a 37°C water bath and washed. Cell concentration was adjusted to $1x10^6$ cells/ml and 10 µl of PDA-001 cells were spiked into an aliquot of BAL fluid cells. Samples were washed with 2.5 ml wash buffer and decanted. Previous experiments have identified the surface marker profile of PDA-001 including the negative expression of pan-hematopoietic marker CD45, erythroid marker CD235a and homogenous high level expression of multiple mesenchymal lineage markers, including CD105, CD10 and CD49c. This multi-parameter profile was shown to distinguish PDA-001 cells from all endogenous cell populations present in human peripheral blood and BAL samples, and could be used for sensitive and specific detection of spiked PDA-001 cells. Staining was performed on ice in the dark then washed twice. Non-viable cells and any debris were excluded relying on the negativity of CD45, CD235a and Forward Scatter and Side Scatter properties. The baseline BAL sample served as a negative assay control, and the baseline BAL spiked with PDA-001 cells *in vitro* served as a positive assay control to determine the assay specificity and optimal gating parameters for the CD45-/CD235a-/CD10+/CD105+/Cd49c+ PDA-001 cell population in each patient sample. Fluorescence Minus One panels were used for negative controls. Data acquisition was performed on a BD Biosciences FACS Canto II flow cytometer and analyzed using FlowJo software.

A posterior anterior chest x-ray was obtained at screening and at days 29, 169, 366, 548, and 731. The individual films from each patient were read by a central reader who was blinded from the timing of chest x-rays during the course of the study. All films were underwent scoring using the system proposed

by Muers et al (15) as previously reported (16). Shadows were categorized as reticulonodular (R) and fibrosis (F). The total profusion score for each lung was obtained by summing the profusion grading from (0 = Absent; 1 = Minimal (just perceptible); 2 = Mild; 3 = Moderate; 4 = Gross) of the four quartiles of the lung. The overall profusion score was the average score of the two lungs.

Results

Four patients were studied. Table 1 summarizes their clinical characteristics. All patients had chronic sarcoidosis, with sarcoidosis diagnosed from 2.5 to 17 years prior to enrollment into the study. During this time, patients had been treated with prednisone and other immunosuppressants as indicated in the table. All patients had experienced a reduction of their FVC over the year prior to study enrollment. Patients had evidence for parenchymal lung disease on basis of chest imaging at the time of study entry.

Table 2 summarizes four biomarkers which were measured at various time points through the first year of the study. These included angiotensin converting enzyme (ACE), soluble IL-2R (SIL2R), vitamin D 1,25 (VITD1,25), and amyloid A. For some patients, there were changes in one of more of these biomarkers after treatment. However, there was no consistent pattern of change through the course of the study for any of these biomarkers.

All four patients received two infusions of 150 million PDA-001 cells. Figure 1 demonstrates the change in FVC during the first year after treatment. There was no significant difference at any of the time points. The same was true for the FEV-1, FEV-1/FVC%, and DLCO (data not shown).

Figure 2 demonstrates the mean PA pressure initially and during the first infusion and for two hours after the infusion. For three of the patients (Patients 1, 2, 4), the PA mean pressure increased by a peak value of 4-6 mm Hg. The rise in PA mean pressure was not associated with any increase in respiratory distress or hypoxemia. Per protocol, pulmonary artery occlusion pressures were not obtained at any time.. One patient (3) developed mild persistent systolic hypertension and tachycardia, which resolved with an oral dose of 25 mg of atenolol. Patient 3 had a 10 mm Hg rise in mean PA pressure (from 14 mm to 24 mm), but as most of this occurred between the first and second measurements, this likely represents a problem with the baseline value. Again,

Table 1. Clinical characteristics of patients at time of treatment

Patient #	1	2	3	4
Age	40	63	41	44
Gender	Male	Female	Male	Male
Self-declared race	African American	Caucasian	Caucasian	African American
Duration of disease prior to study entry (years)	4	2.5	16	17
Change in FVC over year prior to study entry (L)	0.59	0.08	0.31	0.51
Change in FVC over year prior to study entry (absolute change % predicted)	10%	3%	8%	20%
FVC, L (Day1)	2.84	2.73	3.72	2.60
FVC, % predicted	57%	77%	78%	47%
FEV-1, L	1.78	2.09	2.58	1.49
FEV-1/FVC	63%	77%	69%	57%
DLCO, ml/min/mm Hg	13.31	1.307	30.37	16.92
DLCO, % predicted	42%	56%	103%	56%
6MWD, m	351	488	457	457
Chest x-ray stage	3	3	3	2
Extra-pulmonary organ involvement	Liver, Abdominal nodes	None	Skin	None
Initial prednisone dosage, mg/day	10	20	20	10
Initial other immunosuppressives	azathioprine	leflunomide	methotrexate	methotrexate

Table 2. Change in biomarkers over course of study

Day	Normal Range	0	1	8	15	29	57	85	169	366
ACE U/L	0.153-1.139									
Pt1		0.629	0.527	0.629	0.459	0.561	0.493	0.714	0.595	0.578
Pt2		0.51	0.391	0.408	0.493	0.544	0.646	0.51	0.612	0.663
Pt3		0.272	0.306	0.323	0.34	0.323	0.238	0.408	0.391	0.476
Pt4		0.204	0.204	0.34	0.17	0.68	0.323	0.153	0.612	0.102
SIL2R pg/mL	925-3720									
Pt1		1340	1150	1260	1420	1470	1250	1370	883	954
Pt2		2530	2400	3110	3530	3310	2730	2700	2180	3270
Pt3		1790	1710	1910	1840	1590	1850	1470	1440	1590
Pt4		3110	3160	3270	3130	3540	2230	2260	3230	3310
Vit D 1,25 pg/mL	43-173									
Pt1		211	178	96	26	62	ND	115	ND	180
Pt2		127	144	84	113	91	79	106	144	98
Pt3		103	110	137	77	84	62	110	91	60
Pt4		156	154	175	168	139	96	156	142	142
Amyloid A Mg/L	ND									
Pt1		6	5	7	11	4	6	4	8	13
Pt2		41	295	213	388	318	110	38	38	121
Pt3		4	4	6	3	4	3	3	3	3
Pt4		2	1	2	2	1	9	3	2	2
Changes in biomarkes from baseline										
ACE										
Pt1			83.8%	100.0%	73.0%	89.2%	78.4%	113.5%	94.6%	91.9%
Pt2			76.7%	80.0%	96.7%	106.7%	126.7%	100.0%	120.0%	130.0%
Pt3			112.5%	118.8%	125.0%	118.8%	87.5%	150.0%	143.8%	175.0%
Pt4			100.0%	166.7%	83.3%	333.3%	158.3%	75.0%	300.0%	50.0%
SIL2R										
Pt1			85.8%	94.0%	106.0%	109.7%	93.3%	102.2%	65.9%	71.2%
Pt2			94.9%	122.9%	139.5%	130.8%	107.9%	106.7%	86.2%	129.3%
Pt3			95.5%	106.7%	102.8%	88.8%	103.4%	82.1%	80.5%	88.8%
Pt4			101.6%	105.1%	100.6%	113.8%	71.7%	72.7%	103.9%	106.4%
VIT D 1,25										
Pt1			84.4%	45.5%	12.3%	29.4%	ND	54.5%	ND	85.3%
Pt2			113.4%	66.1%	89.0%	71.7%	62.2%	83.5%	113.4%	77.2%
Pt3			106.8%	133.0%	74.8%	81.6%	60.2%	106.8%	88.4%	58.3%
Pt4			98.7%	112.2%	107.7%	89.1%	61.5%	100.0%	91.0%	91.0%
Amyloid A										
Pt1			83.3%	116.7%	183.3%	66.7%	100.0%	66.7%	133.3%	216.7%
Pt2			719.5%	519.5%	946.3%	775.6%	268.3%	92.7%	92.7%	295.1%
Pt3			100.0%	150.0%	75.0%	100.0%	75.0%	75.0%	75.0%	75.0%
Pt4			50.0%	100.0%	100.0%	50.0%	450.0%	150.0%	100.0%	100.0%

ND: not determined; ACE: angiotensin converting enzyme; SIL2R: soluble IL-2R (SIL2R); VIT D 1,25: vitamin D 1,25

this patient had no symptomatic increase in dyspnea associated with the infusion.

Bronchoalveolar lavage (BAL) was performed initially and one day after the second infusion of PDA-001 cells. In three patients, BAL samples from study day 8 were available for FACS analysis. In the remaining case (Patient 2), the BAL sample cell viability was too low for analysis. FACS analysis of the BAL samples (Figure 1) demonstrates the presence of CD10+CD49c+CD105+ cells, indicative of PDA-001 cells. The cells were not detectable in the pre-infusion BAL samples (data not shown). In two of three cases, detectable CD10+CD49c+CD105+ cells were present in the BAL fluid.

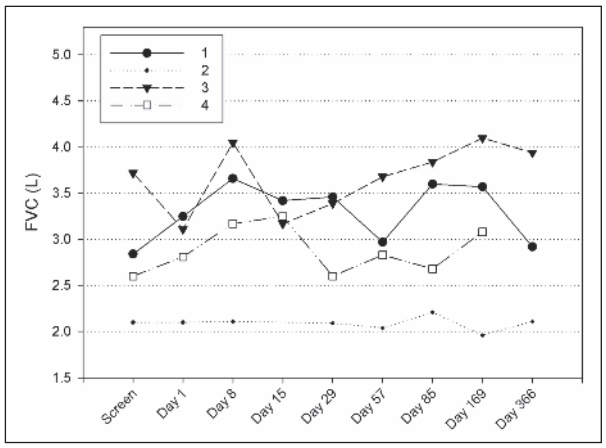

Fig. 1. Forced vital capacity (FVC) of all four patients during the one year of the study. There was no significant change in FVC for any of the four patients

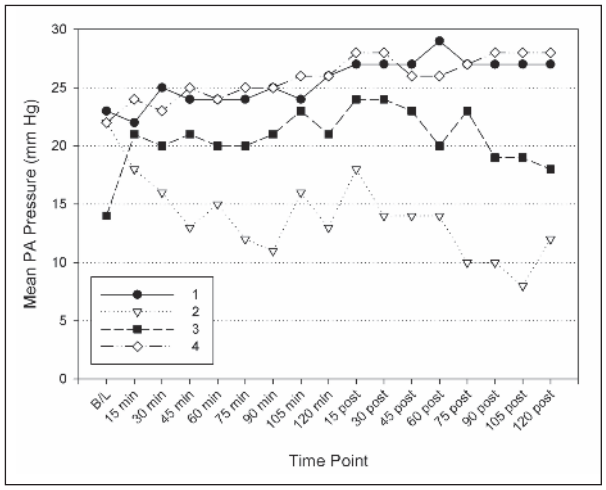

Fig. 2. The mean pulmonary artery pressure (PA mean) initially and for the two hours after initial PDA-001 infusion

All 4 patients had at least 1 treatment-related adverse event. Adverse events seen in at least 2 patients were: arthralgias in 3 patients and chills, fatigue, pyrexia, bronchitis, upper respiratory tract infection, muscle spasm and extremity pain in 2 patients each.

Within six months of study drug infusion, two patients (Patients 3 and 4) had their prednisone and methotrexate withdrawn. At month 12, Patient 3 developed recurrence of chest pain and dyspnea that responded to reinstitution of methotrexate, which he was still taking at 24 months. Patient 4 continued to

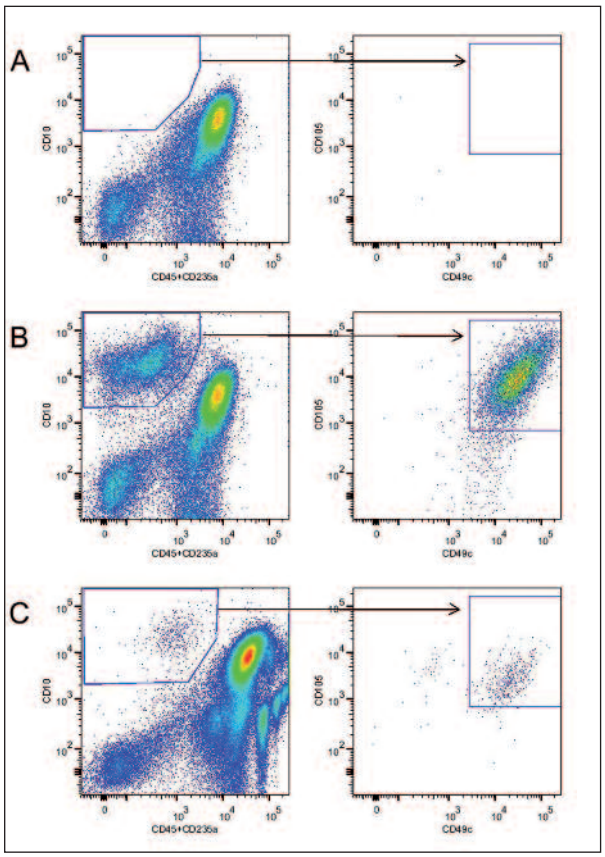

Fig. 3. Representative sample of BAL fluid at baseline and after PDA-001 infusion from Patient x. Panel (A) Baseline BAL fluid, showing no CD10+/CD45-/CD235a- cells were detected. (B) Baseline BAL fluid spiked with $1x10^6$ PDA-001. (C) BAL fluid 2 weeks after cell administration, showing the presence of CD10+/CD45-/CD235a-/CD49c+/CD105+ PDA-001 cells

feel well when taken off all medications and was not receiving either prednisone or methotrexate through month 24.

Figure 4 demonstrates the summation of the R and F score at various time points through the study. Only patients 3 and 4 had a more than 2 point change in their R score. Patient 3 had a small drop in his R score between days 29 and 169 and this persisted through the next 18 months, but rose after day 548, when he had become symptomatic and had methotrexate reinstituted. Patient 4 had a larger drop in his R score between day 29 and 169, which was accompanied by a more than 2 point drop in his F score. While his R score rose again after his prednisone and methotrexate were withdrawn, he had no pulmonary symptoms and his F score remained low.

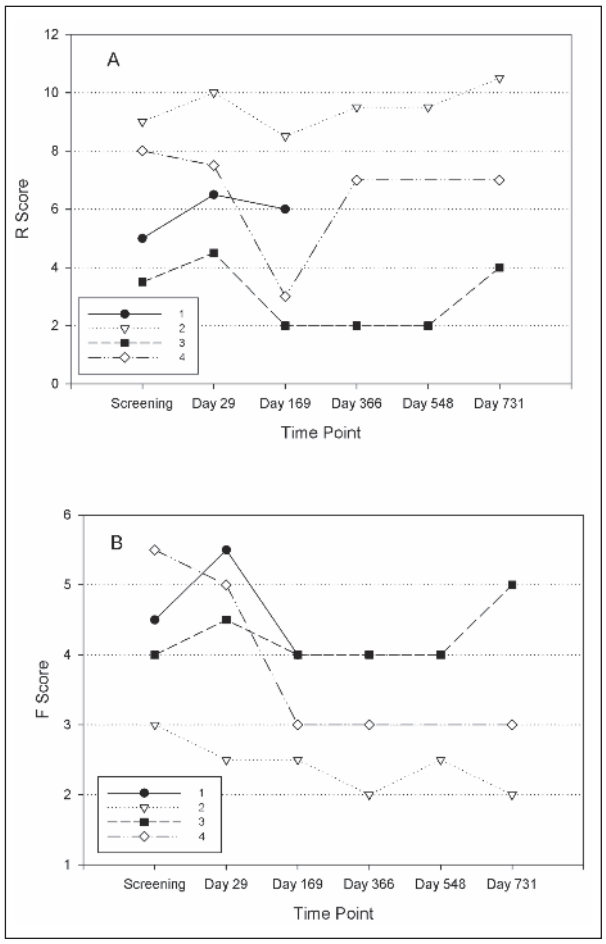

Fig. 4. Changes in Muers (15) R score (3A) and F score (3B) during the course of the study period

One patient (Patient 1) had progression of his disease. He developed a pneumothorax requiring chest tube placement six months after treatment. This was felt to be due to pre-existing bullous disease. He eventually underwent lung transplant because of progressive sarcoidosis, but died of acute rejection one year after study treatment. This event was not believed to be related to PDA-001 administration.

Discussion

PDA-001 cells were administered to four patients with refractory sarcoidosis, as two infusions one week apart. In two cases, the therapy was associated with a prolonged steroid sparing effect that was associated with improvement of the chest roentgenogram. We measured several biomarkers that had been proposed as useful in monitoring sarcoidosis (17). There was no consistent change in any of the biomarkers throughout the first year. The infusions were well tolerated and not associated with clinically significant pulmonary or cardiac symptoms. Examination of the BAL fluid one day after the second PDA-001 administration demonstrated the presence of CD10+CD49c+CD105+ cells (indicative of PDA-001 cells) in two of three cases.

While many patients with sarcoidosis do well within one to two years of diagnosis, there is a group of patients with chronic disease, who continue to require therapy with high doses of glucocorticoids (18, 19) For these patients, several drugs have been proposed (2). Cytotoxic agents such as methotrexate and azathioprine have been shown to be steroid sparing and may lead to mild improvement of pulmonary function (20). Monoclonal antibodies against tumor necrosis factor such as infliximab and adalimumab have been shown to be effective in treating some of these patients (3, 21). However, these drugs appear to be less effective when patients are receiving high doses of glucocorticoids (22).

Placental mesenchymal cell therapy represents a novel treatment option in treating chronic inflammatory diseases. MSCs and MSC-like cells such as PDA-001 have been shown to have anti-inflammatory activity, specifically blocking the Th1 response (6, 8, 23) This includes chronic granulomatous diseases such as Crohn's disease (11, 24, 25). This is the first report of use of placenta-derived cells to treat sarcoidosis.

This current study was designed to test for toxicity of PDA-001 infusion. Patients were given two infusions in a closely monitored setting. No unexpected events were encountered at the time of infusion, or over a two-year follow up period. One patient died one year after initial cell treatment. However, that patient did not have any immediate complications with the cell therapy. He developed increasing respiratory distress six months after treatment and underwent lung transplant about a year after cell therapy. His eventual death was attributed to acute rejection from his lung transplant. None of the four patients in the current study had severe adverse events related to study drug.

A goal of therapy for chronic pulmonary sarcoidosis is to withdraw prednisone and other glucocorticoids (2, 26). In this study, we were able to withdraw corticosteroid therapy in two of four patients. In one case, all treatment for sarcoidosis was withdrawn. For both of these patients there was improvement in the Muers' R and/or F score. The Muers score was developed as a method to determine response to treatment for pulmonary sarcoidosis and has previously been reported as useful in detecting changes after successful treatment of sarcoidosis in placebo controlled trials (15, 16, 27).

In this study, we wished to rule out a possible worsening of pulmonary hypertension associated with the cell therapy infusion. Chronic pulmonary sarcoidosis patients may have pre-capillary hypertension (12). The infusion of cells could lead to micro-emboli and sludging of cells in the pulmonary vasculature. We did note a mild rise in pulmonary pressure after the infusion (Figure 2) that may have been due to the volume expanding effect of the dextran-40 in the cell infusion. Since we did not measure pulmonary artery occluding pressure during this monitoring period, we cannot determine whether this rise in pulmonary artery systolic pressure was due to pre or post capillary hypertension. In all cases the rise in pulmonary artery pressure was not clinically significant and in no case rose above a mean pressure of 30 mm.

Another consideration with the cell therapy is the ability for intravenous infusion to deliver the cells to the alveolar space, the target for therapy in pulmonary sarcoidosis. We were able to demonstrate that in at least two patients, PDA-001 cells were detected in the alveolar space one day after the second treatment. These cells were viable as assessed by FACS.

In conclusion, we demonstrated that treatment with PDA-001 cells in chronic pulmonary sarcoidosis was not associated with clinically significant short or long term toxicity in this small study. While some steroid benefit was observed in two patients, whether this was due to the cell therapy or other factors is unknown. Given the low toxicity and the proof of delivery of cells to the alveolar space, this treatment seems a reasonable approach for further studies.

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