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CLINICAL TRIAL

Human placenta-derived cells (PDA-001) for the treatment of adults with multiple sclerosis: A randomized, placebo-controlled, multiple-dose study ☆

Fred D. Lublin[a,*], James D. Bowen[b], John Huddlestone[c], Marcelo Kremenchutzky[d], Adam Carpenter[e], John R. Corboy[f], Mark S. Freedman[g], Lauren Krupp[h], Corri Paulo[i], Robert J. Hariri[i], Steven A. Fischkoff[i]

[a]*Icahn School of Medicine at Mount Sinai, 5 East 98th Street, Box 1138, New York, NY 10029, United States*
[b]*Swedish Neuroscience Institute, 1600 East Jefferson, Suite 205, Seattle, WA 98122, United States*
[c]*MultiCare Health System-Neuroscience Center of Washington, 915 6th Avenue, Suite 101 and 200, Tacoma, WA 98405, United States*
[d]*London Health Sciences Centre, University Hospital, Multiple Sclerosis Clinic, 7th Floor, 339 Windermere Road, PO Box 5339, London, ON, Canada N6A 5A5*
[e]*University of Minnesota, Clinical Neuroscience Research Unit, 717 Delaware Street SE, Suite 246, Minneapolis, MN 55414, United States*
[f]*University of Colorado Denver, 12631 E. 17th Avenue, Mail Stop B185, Room 5506, Aurora, CO 80045, United States*
[g]*The Ottawa Hospital Multiple Sclerosis Clinic, 501 Smyth Road, Box 607, Ottawa, Ontario, Canada K1H 8L6*
[h]*MS Comprehensive Care Center, MSC T12-020 SUNY, Stony Brook, NY 11794, United States*
[i]*Celgene Cellular Therapeutics, 7 Powderhorn Road, Warren, NJ 07059, United States*

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*Corresponding author. Tel.: +1 212 241 6854; fax: +1 212 241 0440.
E-mail addresses: fred.lublin@mssm.edu (F.D. Lublin), James.Bowen@swedish.org (J.D. Bowen), John.Huddlestone@multicare.org (J. Huddlestone), Marcelo.Kremenchutzky@lhsc.on.ca (M. Kremenchutzky), carpe004@umn.edu (A. Carpenter), John.Corboy@ucdenver.edu (J.R. Corboy), mfreedman@ottawahospital.on.ca (M.S. Freedman), Lauren.Krupp@stonybrook.edu (L. Krupp), cpaulo@celgene.com (C. Paulo), rhariri@celgene.com (R.J. Hariri), sfischkoff@celgene.com (S.A. Fischkoff).

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KEYWORDS
Cell therapy;
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Abstract
Background: Infusion of PDA-001, a preparation of mesenchymal-like cells derived from full-term human placenta, is a new approach in the treatment of patients with multiple sclerosis.
Objective: This safety study aimed to rule out the possibility of paradoxical exacerbation of disease activity by PDA-001 in patients with multiple sclerosis.
Methods: This was a phase 1b, multicenter, randomized, double-blind, placebo-controlled, 2-dose ranging study including patients with relapsing-remitting multiple sclerosis or secondary progressive multiple sclerosis. The study was conducted at 6 sites in the United States and 2 sites in Canada. Patients were randomized 3:1 to receive 2 low-dose infusions of PDA-001 (150×10^6 cells) or placebo, given 1 week apart. After completing this cohort, subsequent patients received high-dose PDA-001 (600×10^6 cells) or placebo. Monthly brain magnetic resonance imaging scans were performed. The primary end point was ruling out the possibility of paradoxical worsening of MS disease activity. This was monitored using Cutter's rule (≥ 5 new gadolinium lesions on 2 consecutive scans) by brain magnetic resonance imaging on a monthly basis for six months and also the frequency of multiple sclerosis relapse.
Results: Ten patients with relapsing-remitting multiple sclerosis and 6 with secondary progressive multiple sclerosis were randomly assigned to treatment: 6 to low-dose PDA-001, 6 to high-dose PDA-001, and 4 to placebo. No patient met Cutter's rule. One patient receiving high-dose PDA-001 had an increase in T2 and gadolinium lesions and in Expanded Disability Status Scale score during a multiple sclerosis flare 5 months after receiving PDA-001. No other patient had an increase in Expanded Disability Status Scale score >0.5, and most had stable or decreasing Expanded Disability Status Scale scores. With high-dose PDA-001, 1 patient experienced a grade 1 anaphylactoid reaction and 1 had grade 2 superficial thrombophlebitis. Other adverse events were mild to moderate and included headache, fatigue, infusion site reactions, and urinary tract infection.
Conclusion: PDA-001 infusions were safe and well tolerated in relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis patients. No paradoxical worsening of lesion counts was noted with either dose.

1. Introduction

Multiple sclerosis (MS) is an immunologically mediated disease of the central nervous system that is prevalent worldwide (Bradley, 2008; Pugliatti et al., 2006; Rosati, 2001). The disease may occur at any age, but onset is most frequent in adults aged 20 to 50 years. MS usually begins as a relapsing, episodic disorder, known as relapsing-remitting MS (RRMS), and for many evolves into a chronic condition characterized by progressive neurologic disability, known as secondary progressive MS (SPMS) (Lublin and Reingold, 1996; Riddell et al., 2011). Several therapies, including biologic agents and immunomodulators, can reduce the relapse rate and formation of new lesions, but no standard therapy is curative (Compston and Coles, 2008; Lublin and Reingold, 1996). No MS therapy to date has shown any significant ability to improve functioning in patients with fixed disability.

Mesenchymal stromal cell-based infusion has the potential to influence both immunomodulation and repair (Darlington et al., 2011; Martino et al., 2010; Nauta and Fibbe, 2007). PDA-001 (cenplacel-L) is a preparation of mesenchymal-like cells derived from healthy, full-term human placental tissue for administration to patients via intravenous infusion (Mayer et al., 2013). The cells display immunomodulatory, anti-inflammatory, pro-regenerative, neuroprotective, and angiogenic properties in preclinical models of neuropathic pain, experimental allergic encephalomyelitis and ischemic stroke (He et al., 2013; Liu et al., 2014; Shehadah et al., 2014). Cultures are expanded as a plastic-adherent, undifferentiated in vitro cell population that expresses the nominal phenotype CD34-, CD10+, CD105+, and CD200+. The cells constitutively express moderate levels of human leukocyte antigen class I and undetectable levels of human leukocyte antigen class II, and do not express the co-stimulatory molecules CD80 and CD86. Cells are genetically stable, displaying a normal diploid chromosome count and normal karyotype, and exhibit normal senescence after prolonged in vitro culture.

In the mouse model for human MS (EAE), administration of PDA-001 exhibits dose-dependent protection from EAE induction and, in established EAE, reduced disease progression and disease severity (Liu et al., 2014). No evidence of a paradoxical worsening was observed with PDA-001, suggesting a low probability that this effect would occur in MS patients. This needs to be confirmed in patients prior to the start of large, Phase II trials. This safety study aimed to rule out the possibility of paradoxical exacerbation of disease activity by PDA-001 in patients with multiple sclerosis. Although not powered for statistical significance, we also looked at preliminary clinical outcome measures. Dose levels selected for the study were based on safety and

efficacy considerations using weight scaling from doses used in the murine EAE model.

2. Methods

2.1. Patients

Patients between 18 and 65 years of age with a pre-existing diagnosis of RRMS or SPMS per the 2005 McDonald Criteria (Polman et al., 2005) and disease duration of at least 2 years were eligible to participate in the study. Patients had to have evidence of active disease as evidenced by clinical progression, continued relapses, or worsening magnetic resonance imaging (MRI) scans after at least 1 year of attempted therapy. The MRI worsening is evidenced by an increase of at least 1 point in Expanded Disability Status Scale (EDSS) score (if screening EDSS was ≤ 5.0) or 0.5 EDSS score (if baseline EDSS was ≥ 5.5). Patients were excluded if they were treated with systemic immunosuppressive medications (eg, infliximab, cyclophosphamide, mitoxantrone, azathioprine, methotrexate, linomide, cyclosporine, cladribine, deoxyspergualin) or natalizumab within 6 months before screening. Adequate cardiac, pulmonary, liver, and renal function was required. All patients gave written informed consent before enrollment.

2.2. Study design

This phase 1b, randomized, double-blind, placebo-controlled, 2-dose escalation study was conducted from November 2010 to August 2011 at 6 sites in the United States and 2 sites in Canada under an Investigational New Drug license from the US Food and Drug Administration and a Clinical Trial Application from Health Canada. The study protocol was approved by local institutional review boards. The study was conducted in accordance with the ethical principles of Good Clinical Practice, as required by independent regulatory authorities and in accordance with the Declaration of Helsinki.

The study sequentially evaluated 2 dosage levels of PDA-001 versus placebo, administered by intravenous infusion. The low-dose (1 unit; 150×10^6 cells) PDA-001 group was enrolled and dosed first; after day 36 evaluation, the Data Monitoring Committee recommended enrollment of the high-dose (4 units; 600×10^6 cells) PDA-001 group. Each dose level cohort consisted of 8 patients, 6 randomized to receive PDA-001 and 2 randomized to receive placebo. A pretreatment screening phase of up to 35 days was followed by an 8-day treatment phase (infusion of PDA-001 or placebo on days 0 and 7), and an initial follow-up phase of 6 months plus an extended follow-up period of 6 months. Patients were followed for the full 12 months regardless of clinical response.

2.3. Assessments

The primary end point was ruling out the possibility of paradoxical worsening of MS disease activity. This was monitored using Cutter's rule (≥ 5 new gadolinium lesions on 2 consecutive scans) by brain magnetic resonance imaging on a monthly basis for six months and also the frequency of multiple sclerosis relapse. Secondary end points included changes in MS-related disability and quality of life.

2.4. Procedures

Patients were assigned to a dose level cohort (8 patients per cohort) based on the order of entry into the study. Using a randomization code generated by an independent statistician, patients were randomly allocated 1:3 to receive low-dose PDA-001, high-dose PDA-001, or placebo and stratified by type of MS (RRMS or SPMS). Treatment was double-blinded, with all patients receiving numbered drug infusion bags that were identical in appearance. All patients and investigators, excluding the pharmacist at each study site, the independent statistician and the independent data monitoring committee, were masked to treatment allocation during the study.

During the screening period, patients were evaluated for study eligibility. Baseline cranial MRI scans were obtained within 14 days before all patients received their initial dose in the treatment phase. PDA-001 and placebo units were supplied in a cryopreserved state. Immediately before administration, units were thawed, reconstituted with sufficient diluent (infusion grade dextran 40) for a total of 240 mL per infusion, and transferred to an infusion bag through the port using sterile technique. Each PDA-001 unit contained approximately 150×10^6 cells. Placebo contained all of the excipients and at the same concentrations as the PDA-001 product, but did not contain the PDA-001 cells.

On study days 0 and 7 of the treatment phase, the first 8 eligible patients (low-dose PDA-001 group) received infusions of 150×10^6 cells or placebo, and then the next 8 eligible patients (high-dose PDA-001 group) received 2 infusions of 600×10^6 cells or placebo. Infusion occurred over 2 h via a 20- to 22-gauge catheter connected to a volumetric infusion pump and had to be completed within 4 h of thaw start time. Diphenhydramine 50 mg and hydrocortisone 50 mg were given as premedications 15 to 30 min before each infusion. Patients' heart rate, respiration, blood pressure, body temperature and blood oxygen saturation were monitored every 15 min during the infusion and for at least 2 h after the end of the infusion. After completing the treatment period, patients entered the initial 6-month follow-up period, during which safety and efficacy data were collected.

Patients received monthly MRI scans for 6 months. MRI data collected during the screening and initial follow-up period were analyzed at a central read facility; this analysis occurred after all patients in the low-dose and high-dose groups completed the initial follow-up period. The extended follow-up period (6 months) allowed for collection of long-term safety data and additional efficacy observations and quality-of-life information. Concomitant MS medications were maintained at a constant dose as long as possible throughout the study.

Data from MRI scans were utilized in the analysis of safety and efficacy end points. MRI data were used to assess the severity of clinical disease by evaluating change in the number of brain MS lesions at 6 months compared with

baseline. The safety evaluation included an on-going review of clinical laboratory tests, including blood and urine; neurological and physical examinations, including vital sign measurements; electrocardiograms; MRI or computed tomography scans of the chest, abdomen and pelvis; use of concomitant medications; and incidence and severity of infusion reactions and adverse events.

The independent data monitoring committee reviewed all safety information to ensure patient safety and determined study continuation and/or modifications. Lesion counts, as determined by local assessment of MRI scans, were provided to the data monitoring committee. These local readings were superseded by the central readings for the final data analysis. The committee was convened upon completion of dosing and month 1 MRI assessments for the low-dose group to review safety information and cranial lesion counts before continuing enrollment into the high-dose group. When a negative safety signal or paradoxical effect was identified, as defined by Cutter's rule (development of ≥ 5 new lesions present on 2 consecutive monthly scans) (Riddell et al., 2011), or ≥ 2 patients experienced a grade 2 or greater allergic reaction, an unexpected treatment-related adverse event or dose-limiting toxicity within 28 days of the initial treatment dose. Dose-limiting toxicity was defined as grade 2 toxicity not resolving within 14 days or grade 3 or greater toxicity at least possibly related to treatment.

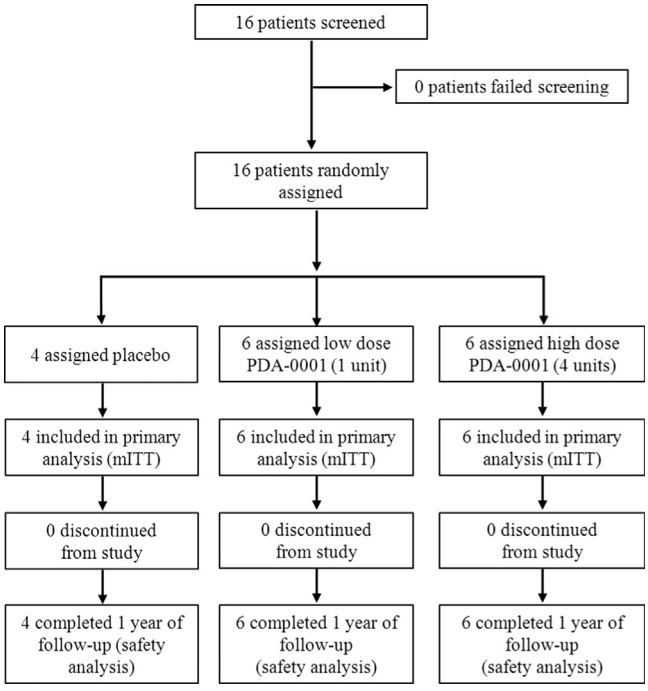

Fig. 1 Trial profile, Abbreviation: mITT, modified intent-to-treat.

The MRI effect was determined by evaluating the number of gadolinium-enhancing lesions over 6 months versus placebo. Changes in clinical function and quality of life were evaluated using a standardized definition of relapse, EDSS, Multiple Sclerosis Functional Composite, MS Fatigue Impact Scale, and the MS Quality of Life scale, which were administered at baseline, before each infusion, monthly during the initial follow-up period, and every 3 months during the extended follow-up period.

2.5. Statistical analysis

The study was not powered to measure efficacy. A sample size of 6 patients per group (low-dose and high-dose PDA-001) was selected to provide preliminary information about safety and clinical effect while minimizing the number of patients exposed to PDA-001 if paradoxical worsening of MS occurred. Data were analyzed after all patients in each cohort completed the initial 6-month follow-up period. The safety population consisted of all patients who received any amount of PDA-001 or placebo. Efficacy analyses were performed on a modified intent-to-treat population, defined as all treated patients with at least 1 follow-up MRI scan. Descriptive summaries were provided for the primary and secondary end points, and no formal statistical tests were planned. Continuous, quantitative, variable summaries

Table 1 Demographics and baseline characteristics.

	PDA-001		Placebo ($n=4$)	Total ($N=16$)
	Low dose, 1 unit ($n=6$)	High dose, 4 units ($n=6$)		
Age, median (range), *y*	52.5 (41-58)	47.5 (36-56)	47.5 (40-52)	48.0 (36-58)
Men, *n* (%)	2 (33)	1 (17)	2 (50)	5 (31)
White race, *n* (%)	6 (100)	6 (100)	4 (100)	16 (100)
Type of MS, *n* (%)				
RRMS	5 (83)	2 (33)	3 (75)	10 (62.5)
SPMS	1 (17)	4 (67)	1 (25)	6 (37.5)
Time since diagnosis, median (range), *y*	6.2 (5.2-31.8)	10.8 (1.0-14.7)	11.35 (2.0-26.5)	8.5 (1.0-31.8)
Gadolinium-enhancing lesions, median (range)	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-1)
EDSS score, median (range)	5.0 (4.0-5.5)	6.0 (1.5-6.5)	4.0 (4.0-4.0)	4.8 (1.5-6.5)

Abbreviations: EDSS, expanded disability status scale; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary-progressive multiple sclerosis.

Table 2 Prior and concomitant multiple sclerosis medications.

Patient number	MS Type	Medication	Prior (P) or concomitant (C)	Start date [study day]	End date [study day]	Reason for use
PDA-001 (1 unit)						
003-1001	RRMS	Glatiramer acetate	P, C	2005	Ongoing	MS
003-1002	RRMS	Interferon-beta-1 A	P, C	2007	Ongoing	MS
		Pregabalin	P, C	2008	Ongoing	Neuropathic pain
		Amitriptyline	P, C	2009	Ongoing	Neuropathic pain
		Baclofen	P, C	2010	Ongoing	Spasticity
003-1004	RRMS	Interferon-beta-1 A	P	2009 [−604]	2010 [−330]	MS
		Gabapentin	C	[72]	Ongoing	MS leg pain
		Cyclobenzaprine	C	[134]	[136]	MS leg pain
		Baclofen	C	[153]	Ongoing	MS leg pain
		Natalizumab	C	[324]	Ongoing	MS
004-1005	RRMS	Fingolimod	P, C	2009 [−495]	Ongoing	RRMS
		Medical marijuana	P, C	2010 [−216]	Ongoing	Spasticity
004-1007	RRMS	Glatiramer acetate	P, C	1998	[173]	RRMS
		Baclofen	P, C	2010 [−453]	Ongoing	MS leg weakness
		Tizanidine	P, C	2010 [−307]	Ongoing	MS leg spasticity
		Fingolimod	C	[193]	Ongoing	RRMS
		Naltrexone	C	[281]	Ongoing	RRMS
007-1008	SPMS	Teriflunomide	P	2007 [−1343]	2010 [−168]	MS
		Amantadine	P, C	2007 [−1385]	Ongoing	MS-related fatigue
PDA-001 (4 units)						
007-2001	SPMS	Natalizumab	P	2009 [−692]	2001 [−184]	MS
005-2003	SPMS	Baclofen	P, C	2004 [−2586]	Ongoing	Muscle spasms
		Gabapentin	P, C	2004 [−2460]	2012 [253]	Neuropathic pain
		Interferon-beta-1A	P, C	2005 [−2201]	2011 [11]	MS
		Prednisolone	P	2011 [−181]	2011 [−179]	MS relapse
002-2004	RRMS	Interferon-beta-1A	P	2006	2011 [−110]	MS
		Interferon-beta-1A	P, C	2011 [−109]	Ongoing	MS
007-2006	SPMS	Amitriptyline	P, C	2011	Ongoing	Muscle spasms
		Gabapentin	P, C	2011	Ongoing	MS-related pain
001-2007	SPMS	Interferon-beta-1A	P, C	2001 [−3,878]	Ongoing	MS
		Glatiramer acetate	P, C	2008 [−987]	Ongoing	MS
		Fampridine	P	2010 [−409]	2011 [−89]	Gait disturbance
		Tizanidine	P	2011 [−147]	2011 [−45]	MS-related spasticity
		Baclofen	P, C	2011 [−76]	Ongoing	MS-related spasticity
006-2008	RRMS	Interferon-beta-1A	P, C	2011	Ongoing	MS

Placebo						
004-1003	RRMS	Gabapentin	C	[50]	Ongoing	MS-related paresthesia
		Pregabalin	C	[128]	Ongoing	Neuropathic pain
004-1006	RRMS	Gabapentin	P, C	2003	Ongoing	MS dysesthesia
		Glatiramer acetate	P, C	2003	Ongoing	RRMS
		Modafinil	P, C	2005	Ongoing	MS-related fatigue
		Vicodin	P, C	2005	Ongoing	MS-related pain
006-2002	SPMS	Interferon-beta-1A	P, C	2003	Ongoing	MS
		Baclofen	P, C	2008 [−938]	Ongoing	MS
		Prednisolone; high-dose intravenous and taper	P	2011 [−108]	2011 [−99]	MS relapse
008-2005	RRMS	Natalizumab	P	2009 [−749]	2010 [−266]	MS
		Fampridine	P, C	2010 [−263]	Ongoing	Mobility
		Prednisolone	P	2011 [−195]	2011 [−193]	MS relapse
		Fingolimod	P, C	2011 [−168]	Ongoing	MS

Abbreviations: MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary-progressive multiple sclerosis.

included the number of subjects, mean, SD, median, minimum, and maximum. Categorical, qualitative, variable summaries included the frequency and percentage of patients in a particular category. All analyses were performed using SAS Software version 9.1 or later (SAS Institute Inc, Cary, NC, USA).

3. Results

Sixteen patients were sequentially screened and randomized into 2-dose level cohorts. Six patients were initially assigned low-dose PDA-001 (1 unit) and 2 were assigned placebo. Subsequently, 6 patients were assigned high-dose PDA-001 (4 units) and 2 were assigned placebo (Fig. 1). All 16 patients completed treatment, the initial 6-month follow-up period and the extended 6-month follow-up period. The safety and modified intent-to-treat populations included all 16 enrolled patients. Baseline disease characteristics were generally well balanced, but the proportion of patients with SPMS was highest in the high-dose PDA-001 group (Table 1). The median baseline EDSS score was 5.0 (range 4.0–5.5) in the low-dose group and 6.0 (range 1.5–6.5) in the high-dose group.

Information on patients' previous failed MS medications before the screening period was not formally collected. Thirteen (81%) patients were taking at least 1 MS medication during the screening and study periods (Table 2). Disease-modifying and symptom-controlling MS medications used by 10% or more of patients during the study were interferon beta-1a (38%), baclofen (31%), glatiramer acetate (25%), gabapentin (19%), and fingolimod (13%). Concomitant medication use was similar between the dose groups.

The gadolinium-enhancing lesion counts (the primary end point) are shown by month in Fig. 2. After 6 months of follow-up, no patient met Cutter's rule, indicating a lack of paradoxical effect of PDA-001 on MS lesions. Cutter's rule required the development of ≥ 5 new lesions present on

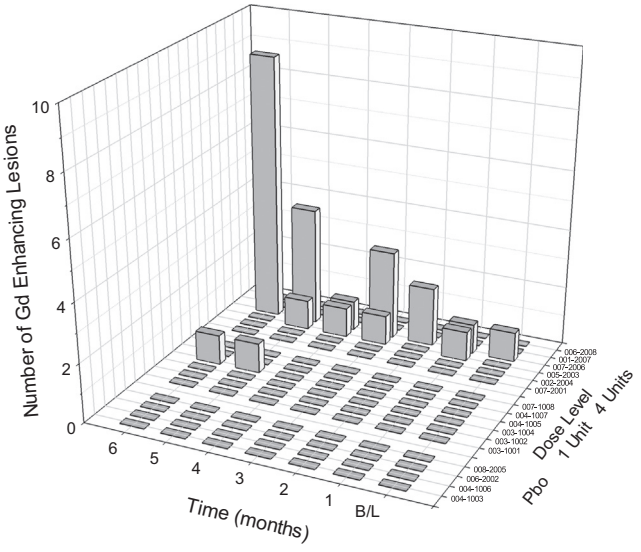

Fig. 2 Magnetic resonance imaging gadolinium-enhancing lesion counts, Abbreviations: B/L, baseline; Pbo, placebo.

2 consecutive monthly scans. One patient showed an increase in gadolinium-enhancing lesions during an MS flare 5 months after receiving high-dose PDA-001 but did not meet Cutter's rule for 2 consecutive scans. This patient also showed an increase in EDSS score during this period (Fig. 3). No other patient had an increase in EDSS score greater than 0.5, and most patients had either stable or decreasing EDSS scores. No trends were seen over time in the Multiple Sclerosis Functional Composite, MS Fatigue Impact Scale, or MS Quality of Life scale.

Adverse events were mild to moderate in intensity (Table 3). The most common adverse events (irrespective of relatedness to study treatment) were headache (44%), upper respiratory infection (31%) and nausea, fatigue, gait disturbance, urinary tract infection, and nasopharyngitis (25% each). Infusion-related adverse events (grade 1 or 2) occurred in 2 patients in the low-dose PDA-001 group and in 4 patients in the high-dose PDA-001 group (38%); these included infusion site swelling (19%), hematoma (12%), site mass (13%), or pain (6%). Serious infusion-related events occurred in 2 patients in the high-dose group (grade 1 anaphylactoid reaction and grade 2 superficial thrombophlebitis), both of which resolved without requiring a change in study medication. Only 1 grade 3 adverse event was reported (MS relapse on day 27; duration, 59 days), but this event was not suspected as being related to study therapy. No patient withdrew from the study due to an adverse event, and no deaths were reported.

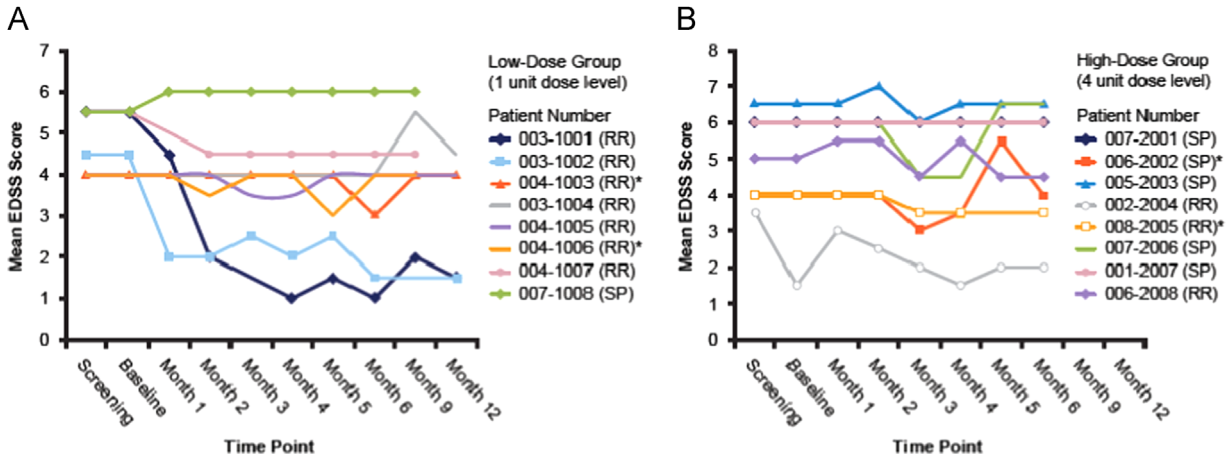

Fig. 3 Expanded disability status scores over a 12-month follow-up period for patients in (A) Low-dose and (B) high-dose Treatment groups, *Patients received placebo. Abbreviations: RR, relapsed-remitting; SP, secondary progressive.

Table 3 Summary of treatment-emergent adverse events.

Parameter	PDA-001		Placebo (n=4)	Total (N=16)
	Low dose, 1 unit (n=6)	High dose, 4 units (n=6)		
Patients with at least 1 AE, n (%)	6 (100)	6 (100)	3 (75)	15 (94)
Highest grade AE				
Mild/grade 1	0 (0)	0 (0)	0 (0)	0 (0)
Moderate/grade 2	6 (100)	5 (83)	3 (75)	14 (88)
Severe/grade 3	0 (0)	1 (17)	0 (0)	1 (6)
Relatedness to study therapy, n (%)				
Suspected	4 (67)	6 (100)	2 (50)	12 (75)
Not suspected	2 (33)	0 (0)	1 (25)	3 (18)
AEs suspected as related to study therapy, n (%)	7	17	3	27
Grade 1/2/3, n (%)	2/5/0	12/5/0	3/0/0	17/10/0
Type of AEs suspected as related to study therapy in $\geq$2 patients in any group (grade 1/2)				
Infusion site swelling	1/1	1	0	3
Headache	0	1/1	0	2
Patients with at least 1 SAE	0 (0%)	2 (33%)[a]	0 (0%)	2 (13%)

Abbreviations: AE, adverse event; SAE, serious adverse event.
[a]Grade 1 anaphylactoid reaction (suspected as related to study therapy); grade 2 superficial thrombophlebitis (not suspected as related to study therapy).

4. Discussion

4.1. Key findings

Infusion of mesenchymal stromal cells or mesenchymal-like cells is a new approach being explored for the treatment of patients with MS and may have immunosuppressive and regenerative potential for damaged neural tissue (Darlington et al., 2011; Keough and Yong, 2013; Uccelli et al., 2011). PDA-001 infusion appears safe and well tolerated in patients with RRMS and SPMS. At the 2 PDA-001 doses tested (1 unit and 4 units), there was no evidence of a paradoxical worsening of MS lesions. EDSS scores over the 1-year follow-up period were similar to baseline or were improved for the majority of patients who received PDA-001, which hints at a potential reparative effect in this disease. No patient experienced a dose-limiting toxicity and no clinically significant safety signals were observed. Adverse events were mild or moderate in severity and included headache, nausea, and infusion site reactions.

4.2. Interpretation

Other cell therapies, including bone marrow-derived mesenchymal stromal cells, have been explored from a safety perspective in patients with MS (Connick et al., 2012; Karussis et al., 2010; Liang et al., 2009; Mohyeddin Bonab et al., 2007). Consistent with these studies, the findings of the current study indicate that infusion of mesenchymal-like cells to patients with MS is feasible and safe. To our knowledge, this phase 1b randomized controlled study is the first to explore clinical effect of placenta-derived mesenchymal-like cell therapy in patients with MS. A recent proof-of-concept phase 2 study with autologous bone-marrow-derived mesenchymal stromal cell infusion in patients with SPMS reported evidence of improvements in some disease-related end points, which was suggestive of neuroprotection (Connick et al., 2012). Relative to cell therapies derived from other tissue sources, PDA-001 may have significant benefits from a novel therapeutic development standpoint, including derivation from a safe and plentiful source of non-embryonic cells (full-term placenta) and production scalability comparable to traditional pharmaceuticals.

4.3. Study strengths and limitations

The precise mechanism by which PDA-001 might act in MS is not known. In the murine EAE model of MS, there is evidence that the therapeutic effect is mediated by both peripheral and central actions (Fisher-Shoval et al., 2012; Morando et al., 2012). PDA-001 modulates immune function in EAE, as well as several other preclinical models of disease (Liu et al., 2014). Collectively, these data provide a scientific rationale for study of PDA-001 in MS and other autoimmune and inflammatory diseases. The development program includes assessment in inflammatory diseases, such as Crohn's disease and arthritis (Mayer et al., 2013). Early phase testing of a disease-modifying reparative strategy for neural damage, as in the immune suppression/reparative strategy for MS, is particularly novel and intriguing. In addition, the potential to repair non-inflammatory neural destruction associated with stroke is being explored (Chen et al., 2013; Shehadah et al., 2014). In the overall PDA-001 development program to date (early studies in all indications), the most common adverse events include headache (29 [26%] of 112 patients), pyrexia (25 [22%] of 112 patients), and nausea (21 [19%] of 112 patients).

The small size of the study precludes any statement about the efficacy of PDA-001 in slowing or reversing the development of disability in these patients. In addition, there was an imbalance in the representation of RRMS and SPMS between the 2 dosing cohorts. The impact of this on our study is unclear; SPMS patients may be less likely to develop new gadolinium enhancing lesions than RRMS patients. However, patient 007-2006, who had the greatest number of new lesions, was an SPMS patient.

5. Conclusion

PDA-001 infusion appears to be safe and well tolerated in patients with MS, and no paradoxical worsening of MS lesion counts was noted in either dose group. Given that no significant negative safety signal was identified, a proof-of-concept study is planned to further evaluate the dose and dosing regimen in patients with RRMS and SPMS.

Authors' contributions

Dr Lublin and Dr Fischkoff had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition of data: All authors.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Fischkoff.

Critical revision of the manuscript for important intellectual content: Lublin, Fischkoff.

Statistical analysis: Fischkoff, Lublin.

Study supervision: Fischkoff.

Conflicts of interest

Drs Lubin, Bowen, Huddlestone, Kremenchutzky, Carpenter, Corboy, Freedman, and Krupp have received grant support from Celgene Corporation. Drs Lublin, Corboy, and Freedman have served as remunerated members of a Celgene advisory committee. Ms Paulo, Dr Hariri, and Dr Fischkoff are full-time employees of Celgene Corporation with stock and stock options.

Role of the funding source

The sponsor was jointly responsible for the study design, along with the other authors. It was also responsible for the study execution, and the data collection and analysis. It was jointly responsible for the writing of the report and the decision to publish this manuscript along with the other authors.

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