CHEST

Original Research

COPD

A Placebo-Controlled, Randomized Trial of Mesenchymal Stem Cells in COPD

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Background: **COPD is a devastating disease affecting millions worldwide. As disease pathogenesis includes both chronic pulmonary and systemic inflammation, antiinflammatory effects of systemically administered mesenchymal stem cells (MSCs) may decrease inflammation, resulting in improved lung function and quality of life. The goal of this study was to assess safety and to perform an initial evaluation of the potential efficacy of systemic MSC administration to patients with moderate to severe COPD.**

Methods: **Sixty-two patients at six sites were randomized to double-blinded IV infusions of either allogeneic MSCs (Prochymal; Osiris Therapeutics Inc) or vehicle control. Patients received four monthly infusions (100×10^6 cells/infusion) and were subsequently followed for 2 years after the first infusion. End points included comprehensive safety evaluation, pulmonary function testing (PFT), and quality-of-life indicators including questionnaires, 6MWT, and assessments of systemic inflammation.**

Results: **All study patients completed the full infusion protocol, and 74% completed the 2-year follow-up. There were no infusional toxicities and no deaths or serious adverse events deemed related to MSC administration. There were no significant differences in the overall number of adverse events, frequency of COPD exacerbations, or worsening of disease in patients treated with MSCs. There were no significant differences in PFTs or quality-of-life indicators; however, an early, significant decrease in levels of circulating C-reactive protein (CRP) was observed in patients treated with MSCs who had elevated CRP levels at study entry.**

Conclusions: **Systemic MSC administration appears to be safe in patients with moderate to severe COPD and provides a basis for subsequent cell therapy investigations.**

Trial registry: **ClinicalTrials.gov; No.: NCT00683722; URL: www.clinicaltrials.gov**

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Abbreviations: 6MWT = 6-min walk test; AE = adverse event; CRP = C-reactive protein; GVHD = graft-vs-host disease; HLA = human leukocyte antigen; IFN-γ = interferon γ; MSC = mesenchymal stem cell; QOL = quality of life; TGF-β = transforming growth factor β; TNF-α = tumor necrosis factor α

COPD, including chronic bronchitis and emphysema, is the third-leading cause of death in the United States, resulting in >126,000 deaths (one in every 20 deaths) in 2005.[1] Further, mortality due to COPD is increasing, and actuarial projections suggest that COPD will be the third-leading cause of death worldwide by the year 2020.[2,3] COPD also has significant economic impact in health-care expenditure and in illness-related decreased productivity. New therapeutic approaches are, thus, desperately needed for COPD.

Mesenchymal stem (stromal) cells (MSCs), isolated from bone marrow, and adipose and other tissues can potently modulate immune-effector cells, including T and B lymphocytes, dendritic cells, and natural killer cells.[4-8] Further, isolated MSCs constitutively express low levels of human leukocyte antigen (HLA) class I and do not constitutively express HLA class II or the cluster of differentiation (CD)40, CD80, and CD86 costimulatory molecules, essential for activation of T-cell immune responses.[6-8] These properties

For editorial comment see page 1525

allow allogeneic MSC administration without donor-recipient HLA matching. Although the full range of mechanisms of MSC actions on inflammatory processes in different diseases has not yet been fully elucidated, there is a growing number of clinical investigations using either autologous or allogeneic MSCs in

immune-mediated diseases, including graft-vs-host disease (GVHD), multiple sclerosis, type 1 diabetes, and others.[9-12]

Previous studies have demonstrated efficacy of both systemic and direct airway MSC administration in rodent models of lung diseases, including COPD.[13-21] We, thus, hypothesized that MSCs would reduce chronic pulmonary and systemic inflammation in patients with COPD with corresponding improvement in pulmonary function and in quality-of-life (QOL) indicators. Prochymal (Osiris Therapeutics Inc) is an investigational agent containing ex vivo-cultured MSCs derived from the bone marrow of healthy adult donors and has demonstrated a strong safety record in previous clinical investigations.[22-25] Prochymal has marketing authorization outside the United States for the indication of GVHD. The primary goal of this study was to assess the safety of systemic MSC administration in patients with moderate to severe COPD. Secondary goals were to evaluate potential efficacy and to assess the effect of MSCs on the level of circulating inflammatory mediators.

Materials and Methods

Study Design and Oversight

A prospective, randomized, double-blind, placebo (vehicle)-controlled design was used, and participants were recruited from six different institutions in the United States. The study was approved by the institutional review board for each participating center and written informed consent obtained from each participant. An independent data and safety monitoring board approved all amendments and oversaw conduct of the trial. The study (NCT00683722) was conducted in accordance with the amended Declaration of Helsinki.[26]

Patient Selection

Eligible patients were 40-80 years of age with moderate to severe COPD (GOLD [Global Initiative for Chronic Lung Disease] stage II or III[27]), smoking history of > 10 pack-years (current or former smokers), postbronchodilator (FEV_1)/(FVC) ratio < 70%, and postbronchodilator FEV_1 between 30% and 70% of predicted value.[27] Major inclusion and exclusion criteria are listed in Table 1.

Study Treatments and Outcomes

Enrolled patients were centrally randomized 1:1 to receive either non-HLA-matched allogeneic MSCs (Prochymal; Osiris Therapeutics Inc) or placebo (vehicle) treatment group. Treatment was administered on days 0, 30, 60, and 90 (Fig 1). MSC dosing was 100×10^6 cells/infusion delivered at a maximum rate of 2.0×10^6 cells/min. Patients treated with placebo received an infusion of vehicle of the same volume as the MSC infusion. Each infusion took approximately 1 h to complete. A description of the study-drug preparation is presented in the e-Appendix 1.

Participants were subsequently evaluated for safety and efficacy until death, withdrawal, or 2 years after the first Prochymal infusion. Safety was assessed by occurrence of adverse events (AEs) during either study-drug infusion or by physician assessments and laboratory evaluations, ECGs during the study, and ECGs during the 2-year follow-up period. A record of COPD exacerbations was maintained for each patient. Efficacy measures included improvement from baseline in pulmonary functions (FEV_1, FVC, FEV_1/FVC,[27] total lung capacity by plethysmography,[27] single-breath carbon monoxide diffusing capacity,[28] exercise performance [6-min walk test (6MWT)], and dyspnea assessment [Borg scale][29,30]), and QOL (St. George's Respiratory Questionnaire,[31,32] and global assessment of patient status). COPD exacerbations were assessed as the time to the first exacerbation and as the ratio of the rate of exacerbations between MSC- and placebo-treated patients. Circulating levels of tumor necrosis factor (TNF)-α, interferon (IFN)-γ, IL-2, transforming growth factor (TGF)-β, IL-4, IL-5, IL-10, and C-reactive protein (CRP) were assessed as markers of systemic inflammation.[33]

Statistical Methods

The number of patients was selected for initial assessment of safety and exploratory evaluation of efficacy in a phase 2 investigation. The study was not powered for efficacy. The study randomized 62 patients in a 1:1 ratio of MSCs to placebo. An analysis of covariance was performed on $FEV_{1\%}$ predicted change from baseline at 6 months, using $FEV_{1\%}$ predicted at baseline as a covariate.[34] For all other end points, statistical analyses were performed using two-sided hypothesis tests, including *t* tests, χ^2 tests, Wilcoxon rank-sum tests, or Fisher exact tests, as appropriate, at the .05 level of significance.[34] Differences in time to first COPD exacerbation and probabilities of being exacerbation free were assessed by Kaplan-Meier methodology and log-rank tests.[34] Total COPD exacerbations experienced per patient, adjusted per exposure, were compared between treatment groups using a two-sided Mantel-Haenszel χ^2 test for ordered categorical data.[34]

Results

Patients

All 62 randomized patients completed all four Prochymal infusions (intent-to-treat population). The baseline characteristics of the intent-to-treat populations are summarized in Table 2 and Table 3. The two treatment groups were generally well matched, although the patients receiving MSCs tended to be older than the patients receiving placebo (mean age,

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Table 1—*Detailed Inclusion and Exclusion Criteria*

Criteria
Inclusion criteria
1. Diagnosis of moderate or severe COPD (stage II or stage III) based on the GOLD standard
2. Postbronchodilator FEV_1/FVC ratio < 3.1
3. Postbronchodilator FEV_1 % predicted value $\geq 30\%$ and $< 70\%$
4. Aged between 40 and 80 y (inclusive), of either sex, and of any race
5. Current or ex-smoker, with a cigarette smoking history ≥ 10 y or > 10 pack-y
Exclusion criteria
1. Asthma or other clinically relevant lung disease other than COPD (eg, restrictive lung disease, sarcoidosis, TB, idiopathic pulmonary fibrosis, bronchiectasis, or lung cancer)
2. Diagnosis of or carrier for α_1-antitrypsin deficiency
3. Body mass ≥ 150 kg or ≤ 40 kg
4. Active infection requiring systemic antibiotic therapy
5. Active *Mycobacterium* infection
6. Significant exacerbation of COPD requiring antibiotics or hospitalization within 4 wk of screening visit
7. Mechanical ventilation within 4 wk of screening
8. Change in absolute FEV_1 from screening to randomization $\geq 20\%$ and ≥ 225 mL
9. Breastfeeding, pregnant, or intends to become pregnant during the study
10. Of childbearing potential and refuses to use an acceptable form of contraception
11. Clinically relevant, uncontrolled medical condition not associated with COPD (eg, hematologic, renal, hepatic, neurologic, or metabolic)
12. AST or ALT ≥ 2.5 times the ULN at screening
13. Bilirubin ≥ 2.0 times the ULN at screening
14. Serum creatinine concentration ≥ 2.0 mg/dL
15. HIV or hepatitis infection
16. Documented history of uncontrolled heart failure as defined by LVEF $\leq 40\%$
17. Left-sided heart etiology of pulmonary hypertension (mitral valve stenosis, left ventricular hypertrophy, any significant left-sided heart disease)
18. Atrial fibrillation or significant congenital heart defect/disease
19. QTc > 450 ms as determined by 12-lead ECG at screening
20. Use of an investigational agent (not approved by the FDA) for any indication within 4 wk of screening visit
21. Use of any TNF inhibitor within 3 mo of screening visit
22. Use of an immunosuppressive medication (eg, azathioprine, methotrexate) that has not been at a stable dose for at least 8 wk prior to screening
23. Use of prednisone ≥ 20 mg/d at any time 4 wk prior to screening visit
24. Pulmonary rehabilitation within 3 mo of screening visit or intent to start pulmonary rehabilitation during the first 6 mo of the study
25. Allergy to bovine or porcine products
26. Evidence of active malignancy, or prior history of active malignancy that has not been in remission for at least 5 y (excludes cutaneous basal cell and squamous cell carcinoma). Subjects with any history of lung cancer are excluded.
27. Significant, active, chronic, inflammatory disease process (eg, active rheumatoid arthritis, collagen vascular disease)
28. Any medical condition that in the opinion of the investigator renders patient's participation in this trial unsuitable
29. Unable to perform all of the assessments required for the study (eg, requires mobility assistance)
30. Life expectancy ≤ 6 mo

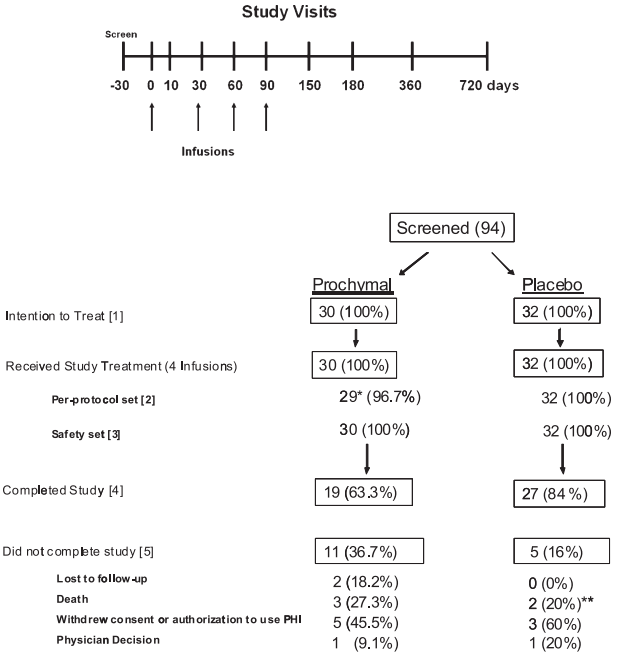

FIGURE 1. Schematics of study design and patient disposition. Time of study-drug infusions are marked by upward arrows. [1] The intent-to-treat set consists of all randomized subjects analyzed in the group to which they were randomized, regardless of actual treatment received. [2] The per-protocol set consists of all randomized subjects who received the correct randomized treatment and did not have major protocol violations. [3] The safety set consists of all randomized subjects who received at least one dose of the study drug, analyzed according to the treatment they received, regardless of randomization. [4] Percentages based on number of randomized subjects (intent-to-treat set). [5] Percentages based on the number of subjects who discontinued prematurely. *One subject failed exclusion criteria due to a > 225 mL change in FEV_1 from visit 1 (screening) to visit 2 (day 0), but was randomized and received the first infusion before the study sponsor (Osiris Therapeutics Inc) was made aware of the deviation. The subject continued in the study, but was excluded from the per-protocol population. **One patient in the placebo group died 2 weeks after the final 2-year study visit and was considered to have completed the study. PHI = protected health information.

68.1 years vs 64.1 years, respectively) and there were more current smokers in the placebo group (37.5% placebo group vs 16.7% MSC group). The patients were comparable in comorbid conditions, severity of COPD (moderate to severe), and in cumulative pack-year smoking history. In general, the enrolled population had relatively advanced disease with 66.1% of patients being categorized as having severe COPD at study entry and an average smoking history of 57.1 pack-years. All patients had at least one clinically significant comorbid condition. Patients in the two treatment groups were relatively well matched with respect to use of medications for COPD (e-Table 1).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; FDA = US Food and Drug Administration; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LVEF = left ventricular ejection fraction; QTc = corrected QT interval; TNF = tumor necrosis factor; ULN = upper limit of normal.

Table 2—*Patient Demographics and Comorbid Conditions*

Demographics	MSC Group (n = 30)	Placebo Group (n = 32)	*P* Value
Age, y	68.1 (7.54)	64.1 (8.76)	.057
Male sex, No. (%)	18 (60)	18 (56)	.765
Race, No. (%)			
White	29 (97)	28 (88)	…
Black	1 (3)	3 (9)	.376
Asian	0	1 (3)	…
Time since diagnosis, y	8.2 (4.4)	7.5 (6.4)	.650
Severe at diagnosis, No. (%)	20 (66.7)	21 (65.6)	.931
Current smokers, No. (%)	5 (16.7)	12 (37.5)	.066
Pack-y smoked	55.9 (21.0)	58.3 (22.0)	.674

Data given as mean (SD) unless otherwise indicated. MSC = mesenchymal stem cell.

All patients in both treatment groups received all four scheduled study infusions and no patient discontinued due to study drug-related AEs. Nineteen of 30 patients (63%) in the MSC group and 27 of 32 (84%) in the placebo group completed the full protocol. Details regarding early termination are given in Figure 1.

Safety Outcomes

Prochymal infusions were well tolerated and no serious or clinically significant AEs were observed over the course of 248 total study-drug infusions (62 patients with four infusions each). No significant changes in oxygen saturations or heart rate were observed during Prochymal infusions (data not shown). Twenty-seven patients (90%) in the MSC group and 28 patients (87.5%) in the placebo group experienced an AE over the full duration of the study protocol. Ten patients (33.3%) in the MSC group and eight patients (25.0%) in the placebo group experienced a serious AE. Events occurring in at least two patients in either group are detailed by system organ class in Table 4. A majority of the AEs were reported as mild to moderate in intensity for both treatment groups (MSCs, 56.6%; placebo, 65.6%). Seven patients (23.3%) receiving MSCs and five receiving placebo (15.6%) reported severe AEs and five patients had fatal AEs: three in the MSC group and two in the placebo group.

A majority of AEs were reported as unlikely related to the study drug (19 [63.3%] in the MSC group vs 22 [68.8%] in the placebo group). The remainder were reported as probably related (four [13.3%] in the MSC group vs 1 [3.1%] in the placebo group) or possibly related (four [13.3%] in the MSC group

Table 3—*Significant Medical History*

Significant Medical History	MSC Group (n = 30)	Placebo Group (n = 32)
Allergies	40	50
Blood/lymphatic	20	19
Cardiovascular	80	81
Endocrine/metabolic	43	47
Gastrointestinal	73	63
Genitourinary	77	88
HEENT	70	75
Hepatic	3	3
Musculoskeletal	77	66
Neurologic	37	31
Psychiatric	53	44
Skin	53	41

Data given as %. HEENT = head, ears, eyes, nose, and throat. See Table 2 legend for expansion of other abbreviation.

Table 4—*Incidence of Adverse Events*[a]

System Organ Class/Preferred Term	Subjects, No. MSCs (n = 30)	Subjects, No. Placebo (n = 32)
Any adverse event	27	28
Cardiac disorders	3	5
Congestive heart failure	2	1
Gastrointestinal disorders	3	5
GERD	0	2
General disorders and administration site conditions	6	2
Peripheral edema	4	0
Immune system disorders	3	0
Seasonal allergy	3	0
Infections and infestations	15	13
Bronchitis	7	5
Nasopharyngitis	0	2
Pneumonia	2	1
Skin infection	0	2
Upper respiratory tract infection	1	4
Urinary tract infection	3	2
Investigations	8	9
Blood calcium increased	1	2
C-reactive protein increased	1	2
Metabolism and nutrition disorders	2	5
Hyperglycemia	0	2
Type 2 diabetes mellitus	0	2
Nervous system disorders	6	7
Dizziness	2	1
Hypoaesthesia	1	2
Lethargy	2	0
Renal and urinary disorders	3	4
Glycosuria	0	2
Hematuria	3	1
Reproductive system and breast disorders	0	2
Benign prostatic hyperplasia	0	2
Respiratory, thoracic and mediastinal disorders	19	14
COPD	14	12
Cough	3	2
Dyspnea	4	2
Emphysema	0	2
Respiratory failure	2	0
Sinus congestion	2	0
Vascular disorders	5	4
Hypertension	1	2

GERD = gastroesophageal reflux disease.
[a]Occurring in at least two subjects.

Table 5—*Relatedness of Adverse Events to Study Drug*

System Organ Class/Preferred Term	Prochymal (n = 30)			Placebo (n = 32)		
	Probable	Possible	Unlikely	Probable	Possible	Unlikely
Any adverse event	0	0	10 (33.3)	0	0	8 (25.0)
Blood and lymphatic system disorders	0	0	1 (3.3)	0	0	0
Anemia	0	0	1 (3.3)	0	0	0
Cardiac disorders	0	0	2 (6.7)	0	0	1 (3.3)
Acute myocardial infarction	0	0	0	0	0	1 (3.3)
Angina pectoris	0	0	1 (3.3)	0	0	0
Supraventricular tachycardia	0	0	1 (3.3)	0	0	0
Gastrointestinal disorders	0	0	0	0	0	1 (3.3)
Umbilical hernia	0	0	0	0	0	1 (3.3)
General disorders and administration site conditions	0	0	1 (3.3)	0	0	1 (3.3)
Asthenia	0	0	1 (3.3)	0	0	1 (3.3)
Infections and infestations	0	0	2 (6.7)	0	0	1 (3.3)
Bronchitis	0	0	0	0	0	1 (3.3)
Pneumonia	0	0	2 (6.7)	0	0	0
Psychiatric disorders	0	0	1 (3.3)	0	0	0
Major depression	0	0	1 (3.3)	0	0	0

Data given as No. (%).

vs five [15.6%] in the placebo group). All of the possibly or probably related AEs were either mild or moderate in severity. No severe or fatal AEs were reported as related to the study drug (Table 5).

Of the five patients who died over the course of the study protocol, all died of respiratory causes, variously coded by the different investigators as COPD, emphysema, or respiratory failure. All deaths occurred at least 1 month after the final Prochymal infusion and one death in the placebo group occurred 2 weeks after the final 2-year study visit.

There were isolated instances of laboratory values, ECGs, or physical examination findings shifting from normal to abnormal at 1 year and 2 years. These instances were of similar prevalence in the MSC and placebo groups. ECG results from the 6-month visits showed no significant cardiopulmonary changes compared with baseline in patients receiving either MSCs or placebo. At baseline (screening ECG), the mean pulmonary arterial pressure was 29.88 ± 11.37 mm Hg for patients treated with MSCs, and 25.53 ± 13.59 for patients receiving placebo. At 6 months, the pulmonary pressure decreased on average 1.58 ± 12.72 mm Hg in the MSC group and 0.376 ± 16.69 mm Hg in the placebo group.

Efficacy Outcomes

No statistically significant differences in FEV_1 or $FEV_{1\%}$ predicted were observed through 2 years (Fig 2), nor were there observed differences between the groups in FVC, FVC% predicted, total lung capacity, or carbon monoxide diffusing capacity from baseline to 1 year or 2 years (Fig 2, e-Table 2). No statistically significant or clinically meaningful differences between the two treatment groups were observed in the 6MWT, St. George's Respiratory Questionnaire, or Borg Dyspnea Scale scores (post-test minus pretest) from day 10 to 2 years (Fig 2), or in the physicians' global assessments (data not shown). There were no significant differences in oxygen saturations between the study groups during the 6MWTs during the study visits (e-Tables 3, 4). There was no significant difference in the number of patients with COPD exacerbations (20 [66.7%] in the MSC group vs 15 [46.9%] in the placebo group). Only a small number of patients were hospitalized for COPD exacerbations during the study protocol (six in the MSC group vs five in the placebo group), and no meaningful comparison could be made. Median time to first exacerbation was 6.7 months in the MSC group; this could not be estimated for the placebo group due to the smaller number of patients reporting exacerbations. At 1 and 2 years, the probability of being exacerbation free was 46.0% and 31.9%, respectively, in the MSC group vs 56.3% and 52.7%, respectively, in the placebo group. However, the CIs around the probabilities of being exacerbation free at both visits overlapped for the two groups, indicating that the differences were not statistically significant. Review of patients' diaries revealed that reliever/rescue medication use was not systematically recorded and it was not possible to do the planned analyses.

Levels of circulating TNF-α, IFN-γ, IL-2, IL-4, IL-5, and IL-10 were at or below limits of assay detection in most study patients, precluding meaningful analyses. Levels of circulating TGF-β and CRP did not differ significantly between baseline to years 1 or 2 in either treatment group (Table 6, e-Table 4). However, post hoc analysis of patients with elevated, circulating CRP levels at baseline (> 4.0 mg/L in 29 of 62 patients [14 in the MSC group, 15 in the

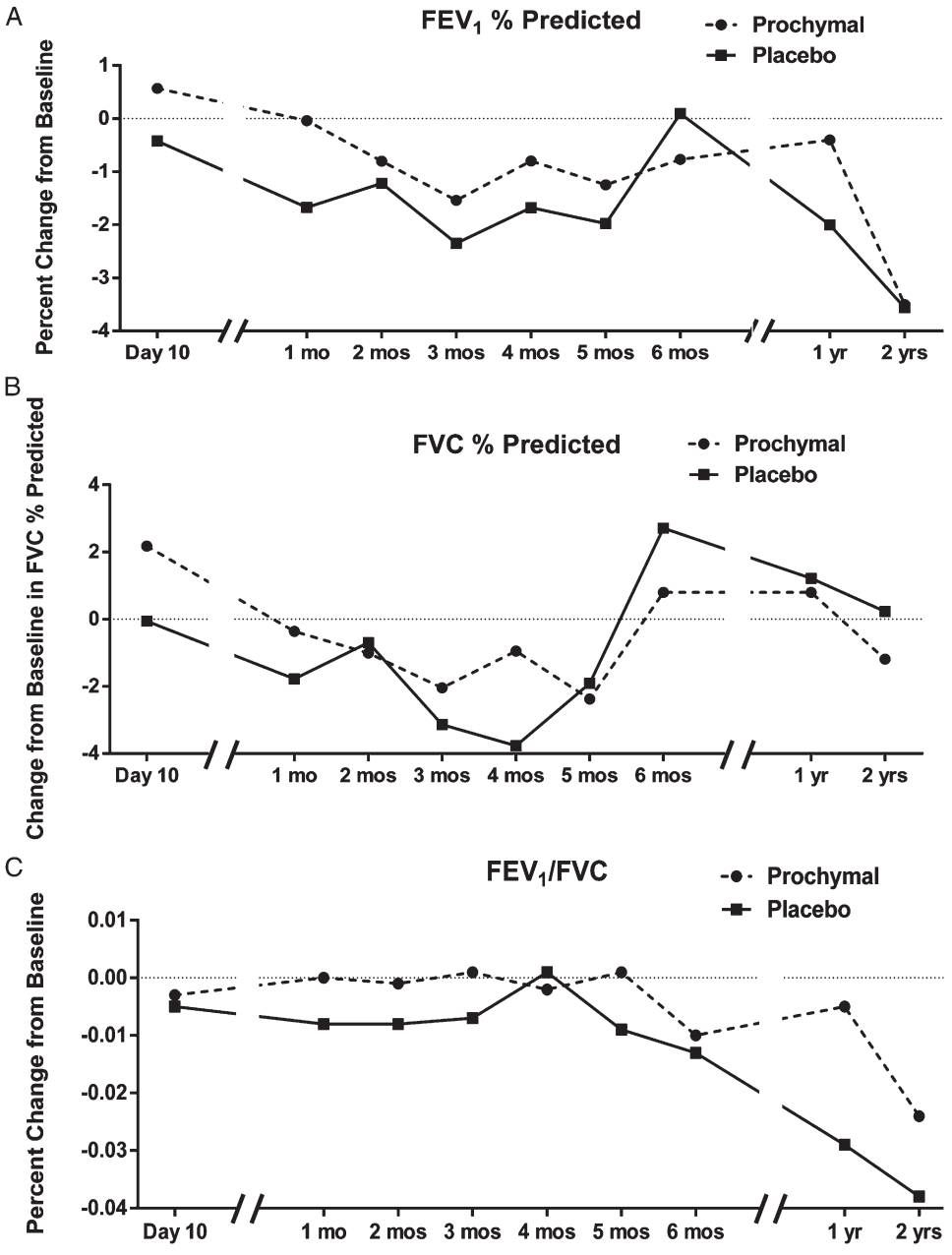

FIGURE 2. A-F, Changes in (A) $FEV_{1\%}$ predicted, (B) FVC % predicted, (C) FEV_1/FVC, (D) 6MWT, (E) Borg dyspnea scale, and (F) circulating CRP levels in the study populations. Changes in circulating CRP levels are shown only for those who had elevated levels at screening (>4.0 mg/L). *$P < .05$. 6MWT = 6-min walk test; CRP = c-reactive protein.

placebo group]) demonstrated a statistically significant decrease in circulating CRP at 1 month after the first infusion in patients receiving MSCs. This numerical trend continued for the duration of the study period (Fig 2).

DISCUSSION

Administration of either autologous or non-HLA-matched allogeneic MSCs is increasingly being investigated as a potential therapeutic intervention for a range of inflammatory and immune diseases. Clinical trials to date have demonstrated safety of systemic MSC infusion and, thus far, there do not appear to be any significant AEs in follow-up periods lasting for several years in a variety of patient populations.[9-12,35] Concerns of special interest, including ectopic tissue formation, tumor development, or infusional toxicities, have not been observed to date. Notably, review of autopsy findings in patients with GVHD who had received allogeneic MSCs demonstrated minimal presence of residual MSCs up to 577 days after administration.[36] Most clinical investigations have used MSCs of bone marrow origin, but MSCs isolated from

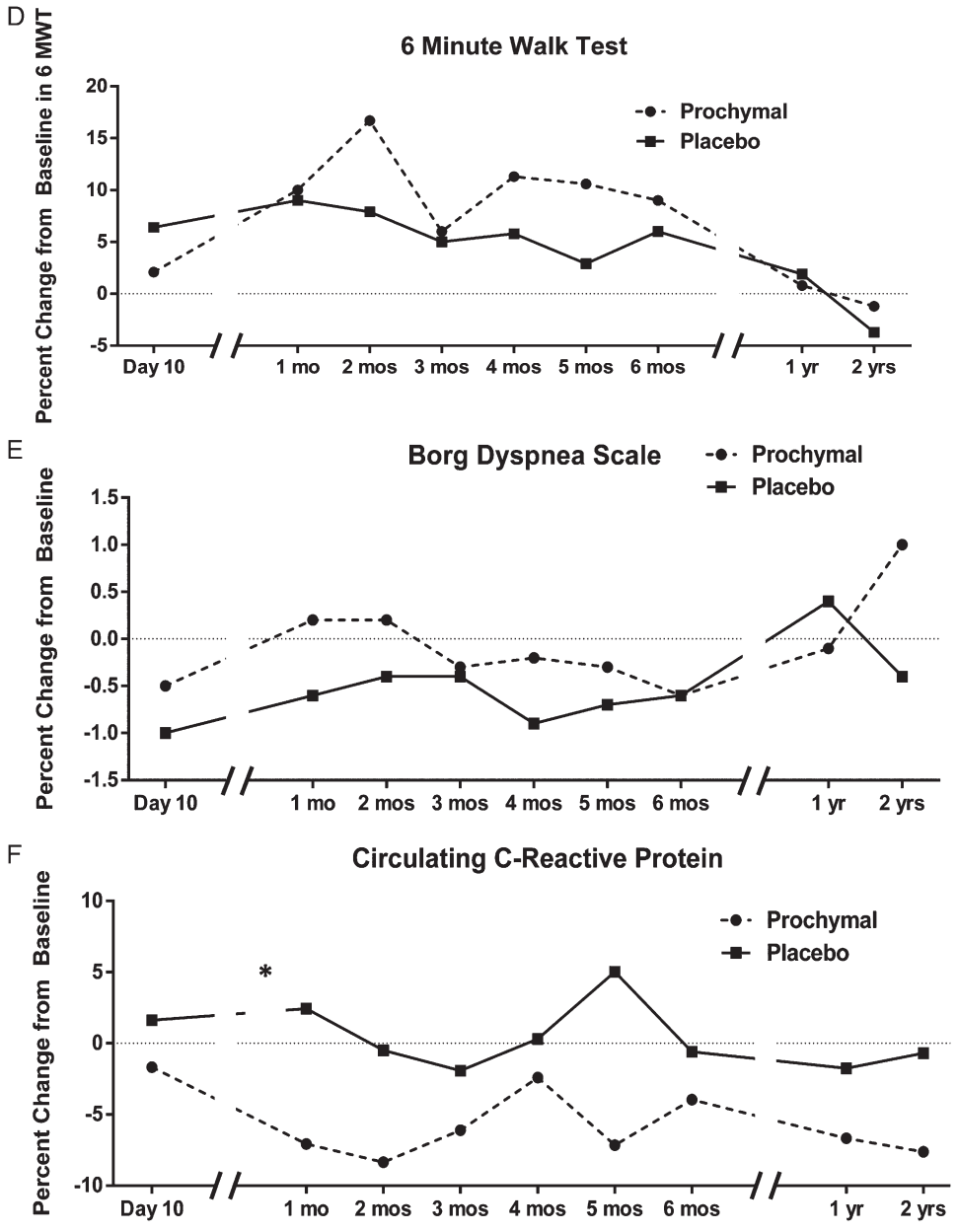

Figure 2. Continued.

adipose tissue, placenta, and other sources are also being evaluated. While the mechanisms of action are not completely understood, MSCs from any of these sources can have a range of anti-inflammatory effects, including release of soluble anti-inflammatory molecules and activation of cellular anti-inflammatory pathways in different inflammatory environments.[6-8,37,38] These actions fit with the postulated physiologic roles of MSCs in regulating the inflammatory environment in the bone marrow stroma and as perivascular cells regulating systemic inflammation.[9,39,40]

COPD encompasses a spectrum of heterogeneous disorders that can include both destructive emphysematous changes and thickened bronchiolar walls with variable luminal mucus occlusion, as well as chronic pulmonary and systemic inflammation. A study of MSC administration in patients with acute myocardial infarction suggested an improvement in FEV_1 and FVC in treated patients.[24] In parallel, a growing number of preclinical studies have demonstrated efficacy of both systemic and direct airway MSC administration in rodent models of inflammatory and emphysematous lung injuries resulting from chronic cigarette smoke-extract exposure or from exposure to destructive or inflammatory substances such as elastase or papain.[13-21] In each model, MSCs inhibit inflammation and decrease or reverse destructive emphysematous changes. While these rodent models

Table 6—*Mean Levels of Circulating CRP and TGF-β in the Intent-to-Treat Study Populations*

	CRP, ng/mL		TGF-β, ng/mL	
Study Days	Prochymal	Placebo	Prochymal	Placebo
Day 0	7.55	6.38	38,555	36,853
Day 10	6.87	6.17	39,269	39,534
1 mo	4.97	6.58	40,513	40.985
2 mo	5.57	4.68	41,799	42,147
3 mo	4.94	3.88	41,689	36,625
4 mo	6.68	5.22	41,637	34,331
5 mo	4.24	7.03	43,065	34,165
6 mo	9.76	6.56	37,425	31,998
1 yr	5.63	3.42	34,623	30,709
2 yr	5.68	4.26	44,936	35,914

CRP = C-reactive protein; TGF = transforming growth factor.

do not fully reflect clinical disease, the results suggest that MSCs can inhibit the chronic pulmonary and systemic inflammation characteristic of COPD. The observed decrease in CRP levels in MSC-treated patients with elevated circulating CRP at baseline in the current study suggests that this may indeed be the case.

Importantly, the current study demonstrates safety of MSC administration in an older population of patients with moderate to severe COPD as well as multiple comorbidities. No infusional toxicity, significant serious AEs, or attributable deaths were seen in the patients treated with MSCs. No clinical signs or symptoms of pulmonary emboli were observed during the study-drug infusions. These important observations demonstrate that by using a tolerable dose and infusion rate, multiple MSC infusions are safe in a population of patients with compromised lung function and provide a firm platform for use of MSCs in further clinical investigations in COPD and other lung diseases.

No significant effects of MSC infusions were observed on pulmonary function or QOL indicators. Further larger-scale trials will be necessary to more fully examine potential effects of MSCs on these and other clinical assessments in this patient population. Other factors may have influenced potential MSC efficacy in the current trial. For example, the dosing and treatment schedules used were empirically based on data from MSC trials in other diseases[22,24] and may not be effective in chronic lung diseases. Further, MSCs may not be effective in decreasing the full spectrum of pathophysiology that contributes to the clinical manifestations of COPD, including chronic, progressive, structural tissue damage. More acute diseases of lung inflammation (eg, ARDS) may be more amenable to the intense, short-lived, anti-inflammatory effects of administered MSCs.[13,41,42] Similarly, chronic immune-based inflammatory lung diseases, such as severe steroid-refractory asthma, may also be better targets.[13,38,43] Nonetheless, given the substantial human and economic burdens of COPD and the compelling need for new therapies, further investigations of MSC therapies are warranted.

In summary, systemic administration of multiple doses of MSCs appears to be safe and may decrease inflammation in an older, comorbid population of patients with compromised lung function due to moderate to severe COPD. These results provide an important and significant basis for further clinical investigations of MSCs in patients with COPD and other lung diseases.

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Author contributions: Dr Weiss had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Weiss: contributed to study design, data acquisition and interpretation, drafting and revising the article, and final approval of the article; and served as principle author.
Dr Casaburi: contributed to data acquisition and interpretation, drafting and revising the article, and final approval of the article.
Ms Flannery: contributed to study conception and design, data interpretation, drafting and revising the article, and final approval of the article.
Dr Williams: contributed to study conception and design, data interpretation, revising the article, and final approval of the article.
Dr Tashkin: contributed to data acquisition and interpretation, drafting and revising the article, and final approval of the article.
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Role of sponsor: Osiris Therapeutics Inc provided funding for the investigation and was involved in the study conception and design, data interpretation, article revision, and final approval of the manuscript.
Other contributions: A list of participating sites and personnel is available in e-Appendix 2.
Additional information: The e-Appendixes and e-Tables can be found in the "Supplemental Materials" area of the online article.

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