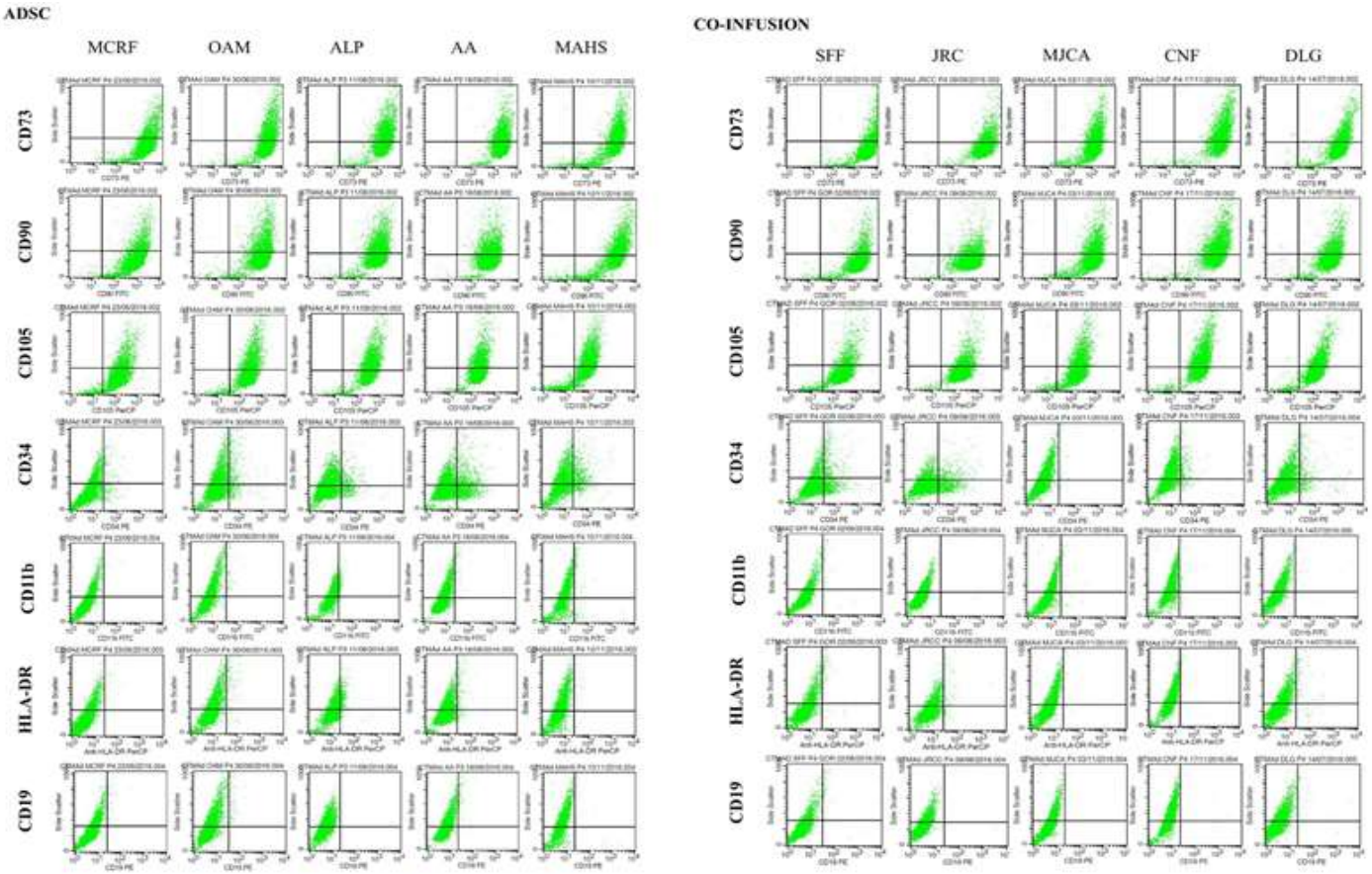
Supplementary Data and Tables

Supplementary Data S1 - Randomization process

The method consisted of the following steps: Initially a random allocation list of 20 sequential numbers was generated in 4 groups of 5 numbers through the specialized website https://www.sealedenvelope.com/simple-randomiser/v1/lists [Accessed 7 Dec 2015]. The four study groups were named Group 1 = Control, Group 2 = Bone Marrow, Group 3 = Adipose tissue and Group 4 = Co-infusion. An independent IEP-São Lucas (SP, Brazil) researcher made 20 cards numbered from 1 to 20 on carton board that was folded and placed in 20 identical envelopes. The envelopes were sent to the independent researcher at the Pulmonology Outpatient Clinic at ABC Medical School (FMABC - Santo André, SP, Brazil) who checked the 20 envelopes. The selected participants were summoned to choose 1 envelope and open it in the presence of the independent researcher and witnesses. The independent researcher from the Outpatient Clinic called the telephone number of the independent researcher of the IEP-São Lucas who informed the identification of the group corresponding to the number drawn by the participant. The independent researcher at the Pulmonary Outpatient Clinic at FMABC reported the outcome of the randomized group to the patient and to the study researchers who recorded it in the patient's chart**.**



Supplementary Figure 1. Gating strategy used to identify the cells on ADSC and Co-infusion groups.

Legend: ADSC, adipose-derived mesenchymal stromal cells; subjects coded identifications, MCRF, OAM, ALP, AA, MAHS, SFF, JRC, MJCA, CNF, DLG; immunophenotypic markers (CD), CD73, CD90, CD105, CD34, CD11b, HLA-DR, CD19.

Supplementary Table S1 Pre and post-treatment laboratory evaluation and clinical follow-up of patients

Evaluated Parameters	Pre-procedure	Procedure	Visits post-procedure						
			7 D	1 M	2 M	3 M	6 M	9 M	12 M
Clinical evaluation	X	X	X	X	X	X	X	X	X
mMRC Dyspnea Scale	X	X	X	X	X	X	X	X	X
6 Minute Walk Test (6MWT)	X			X		X	X	X	X
Thorax radiography	X			X				X	
Chest computed tomography	X						X		X
Post-bronchodilator spirometry	X					X	X		X
Pulmonary volumes by plethysmography	X					X	X		X
CO diffusion	X						X		X
Doppler cardiogram	X								X
Cardiopulmonary test	X						X		X
Ventilation/perfusion scintigraphy	X								X
Urine I, coagulogram	X								
Anti-HIV, hepatitis B and C, syphilis	X								
Arterial blood gas analysis	X			X		X			X
Complete blood count, renal function sodium, potassium, urea, and creatinine	X		X	X	X	X	X	X	X
Inflammatory markers: CRP	X		X	X		X	X	X	X
Tumor marker CEA	X			X			X		X
Liver function: AST, ALT, GGT	X								X

Abbreviations: D, days; M, months; mMRC, Modified Medical Research Council (Dyspnea scale; CO, carbon monoxide; HIV, human immunodeficiency virus; CRP, C-reactive protein; CEA, carcinoembryonic antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase.

Supplementary Table S2 Cell viability test and immunophenotypic markers (CD) for ADSC

			Surface markers (CD) (%)							
Group	Patient	Viability (%)	CD73/ CD90	CD73/ CD105	CD90/ CD105	CD34	CD45	CD11b	HLA-DR	CD19
ADSC	MCRF	96·38	99·43	97·52	98·12	0·90	2·48	0·08	0·02	0·02
ADSC	OAM	97·56	99·12	98·75	98·61	0·94	1·39	0·04	0·02	0·00
ADSC	ALP	93·82	99·84	99·72	99·72	1·47	0·28	0·07	0·00	0·00
ADSC	AA	96·66	99·90	99·88	99·84	1·26	0·16	0·00	0·12	0·02
ADSC	MAHS	98·26	98·97	96·48	96·83	1·54	3·52	0·17	0·00	0·08
Co-infusion	SFF	96·25	99·34	97·79	98·13	0·91	2·21	0·08	0·02	0·04
Co-infusion	JRC	95·58	98·84	98·74	97·92	1·85	2·08	0·04	0·02	0·03
Co-infusion	MJCA	98·26	99·90	99·62	99·78	0·13	0·38	0·08	0·08	0·00
Co-infusion	CNF	97·31	99·20	98·11	98·11	1·43	1·89	0·09	0·06	0·02
Co-infusion	DLG	92·08	99·42	98·20	98·46	0·89	1·80	0·02	0·00	0·00
Mean		96·22	99·40	98·48	98·55	1·13	1·62	0·07	0·03	0·02
SD		1·97	0·38	1·08	0·97	0·48	1·08	0·05	0·04	003

Abbreviations: ADSC, adipose-derived stromal cells; CD, cluster of differentiation; SD, standard deviation.

Supplementary Table S3 Cell viability test and immunophenotypic markers (CD) for bone marrow mononuclear cells - (BMMC)

Group	Patients	Viability (%)	Mononuclear cells (MNC) %	CD45+CD34+
BMMC	MLO	98·75	53·53	2·02
BMMC	AMIH	97·88	26·20	1·33
BMMC	MCB	98·74	17·35	0·43
BMMC	ELL	98·54	10·92	0·51
BMMC	JSF	97·89	30·74	1·73
Co-infusion	SFF	95·50	40·12	1·15
Co-infusion	JRC	95·56	30·58	0·90
Co-infusion	MJCA	96·73	48·87	0·56
Co-infusion	CNF	98·10	28·66	0·56
Co-infusion	DLG	97·95	46·96	2·40
Mean		97·56	33·39	1·16
SD		1·22	13·85	0·70

Abbreviations: BMMC, bone marrow mononuclear cells; SD, standard deviation.

Supplementary Table S4 Spirometry FEV1 (%) post-bronchodilator

	Months							
	0		3		6		12	
Group	μ	SD	μ	SD	μ	SD	M	SD
Control	41·80	7·95	48·33	12·86	44·00	13·66	43·60	12·62
BMMC	39·60	6·99	39·80	8·81	38·00	8·37	43·75	12·61
ADSC	38·76	5·74	43·60	19·11	34·60	8·62	34·60	8·32
Co-infusion	39·40	6·35	39·00	2·65	37·67	8·33	36·25	4·57

Abbreviations: FEV_1, forced expiratory volume in the first second; BMMC, bone marrow mononuclear cell; ADSC, adipose-derived mesenchymal stromal cells; μ, mean; SD, standard deviation.

Supplementary Table S5 Spirometry FEV1/FVC (%)

	Months							
	0		3		6		12	
Group	μ	SD	μ	SD	μ	SD	M	SD
Control	66·20	13·48	51·33	11·02	47·75	7·72	49·60	7·44
BMMC	64·56	10·83	46·00	12·21	51·46	11·00	56·25	22·65
ADSC	63·56	15·09	48·40	9·86	45·40	6·99	46·60	8·56
Co-infusion	52·00	10·98	42·67	10·97	41·00	11·53	39·75	10·78

Abbreviations: FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; BMMC, bone marrow mononuclear cell; ADSC, adipose-derived mesenchymal stromal cells; μ, mean; SD, standard deviation.

Supplementary Table S6 Plethysmography TLC (%)

	Months							
	0		3		6		12	
Group	μ	SD	μ	SD	μ	SD	M	SD
Control	127·60	11·10	133·33	5·03	132·00	6·24	129·20	14·11
BMMC	121·60	15·16	124·75	15·65	131·40	18·39	134·25	26·54
ADSC	89·69	51·79	92·87	52·81	92·09	54·30	87·07	49·32
Co-infusion	142·50	21·98	145·00	2·65	134·00	21·52	140·50	16·58

Abbreviations: TLC, total lung capacity; BMMC, bone marrow mononuclear cell; ADSC, adipose-derived mesenchymal stromal cells; μ, mean; SD, standard deviation.

Supplementary Table S7 Plethysmography RV (%)

	Months							
	0		3		6		12	
Group	μ	SD	μ	SD	μ	SD	M	SD
Control	215·60	46·63	221·67	21·39	227·00	59·41	218·40	59·26
BMMC	210·00	26·30	211·50	50·36	230·60	43·44	232·75	72·50
ADSC	151·11	85·64	158·68	89·04	162·15	93·96	144·73	81·21
Co-infusion	233·00	49·30	224·00	74·36	239·67	44·24	230·75	63·76

Abbreviations: RV, residual volume; BMMC, bone marrow mononuclear cell; ADSC, adipose-derived mesenchymal stromal cells; μ, mean; SD, standard deviation.

Supplementary Table S8 Plethysmography RV/TLC (%)

	Months							
	0		3		6		12	
Group	μ	SD	μ	SD	μ	SD	M	SD
Control	195·80	33·80	198·00	13·86	188·67	52·97	192·00	34·39
BMMC	186·60	23·32	195·75	31·44	195·60	25·15	198·75	36·45
ADSC	156·83	91·69	159·05	92·34	163·46	92·28	154·48	88·89
Co-infusion	183·25	42·85	177·67	68·09	197·67	28·36	179·50	50·00

Abbreviations: RV, residual volume; TLC, total lung capacity; BMMC, bone marrow mononuclear cell; ADSC, adipose-derived mesenchymal stromal cells; μ, mean; SD, standard deviation.

Supplementary Table S9 Plethysmography DLCO (%)

	Months							
	0		3		6		12	
Group	μ	SD	μ	SD	μ	SD	M	SD
Control	47·60	26·99	54·00	22·61	56·25	23·92	48·80	22·08
BMMC	35·92	26·92	60·25	24·10	61·25	27·84	64·00	20·52
ADSC	43·40	30·71	52·40	21·00	54·20	23·64	48·00	19·89
Co-infusion	35·60	11·15	38·33	11·59	51·33	17·90	47·00	21·95

Abbreviations: DLCO - diffusion lung capacity for carbon monoxide; BMMC, bone marrow mononuclear cell; ADSC, adipose-derived mesenchymal stromal cells; μ, mean; SD, standard deviation.

Supplementary Table S10 Plethysmography Raw (%)

	Months							
	0		3		6		12	
Group	M	SD	μ	SD	μ	SD	M	SD
Control	164·00	47·81	145·33	21·36	177·33	42·52	169·00	63·75
BMMC	194·50	80·14	185·25	69·36	200·50	67·00	137·67	60·35
ADSC	150·18	97·39	141·98	93·38	173·16	106·23	144·15	87·81
Co-infusion	151·00	0·45	158·33	26·16	174·67	19·50	185·00	25·31

Abbreviations: Raw, airway resistance; BMMC, bone marrow mononuclear cell; ADSC, adipose-derived mesenchymal stromal cells; μ, mean; SD, standard deviation.

Supplementary Table S11 Plethysmography pCO_2

	Months							
	0		1		6		12	
Group	M	SD	μ	SD	μ	SD	M	SD
Control	35·86	2·74	36·28	3·95	37·85	2·68	34·54	4·22
BMMC	36·22	4·56	35·04	3·76	34·54	4·58	34·90	2·62
ADSC	37·04	3·87	38·90	3·26	38·30	3·57	35·53	5·38
Co-infusion	37·10	3·94	36·83	3·18	38·35	2·90	37·23	5·25

Abbreviations: pCO_2, partial pressure of CO_2; BMMC, bone marrow mononuclear cell; ADSC, adipose-derived mesenchymal stromal cells; μ, mean; SD, standard deviation.

Supplementary Table S12 Scintigraphy of the right and left lungs of the control and treated patients, comparing the pre-treatment values and at the end of 12 months of follow-up

Treatment	Right lung			Left lung		
	Pre-treatment	12 months	Difference	Pre-treatment	12 months	Difference
BMMC	50·73 ± 2·94	50·07 ± 1·32	-0·66	49·27 ± 2·93	49·93 ± 1·31	0·66
ADSC	54·59 ± 3·73	54·11 ± 2·81	-0·48	45·41 ± 3·73	45·89 ± 2·81	0·48
Co-infusion	49·13 ± 0·98	49·51 ± 1·33	0·38	50·87 ± 0·98	50·49 ± 1·33	-0·38
Control	52·42 ± 4·17	53·40 ± 3·08	0·98	47·57 ± 4·17	46·59 ± 3·08	-0·98

Abbreviations: BMMC, bone marrow mononuclear cell; ADSC, adipose-derived mesenchymal stromal cells.

Supplementary Table S13 Analysis of results for different pulmonary function parameters over 12 months in relation to baseline data before treatment for the Control, BMMC, ADSC and Co-infusion groups

			Δ (%)			
	Basal (L)	**Basal (%)**	**Basal - 3 months**	**3 - 6 months**	**6 - 12 months**	**Basal - 12 months**
Total lung capacity (TLC)						
Control	617 ± 0·8	127 ± 11	0·16 (0·09; 0·39)[a]	-0·18 (-0·18; -0·18)[a]	0·17 (-0·15; 0·49)	0·4 (-0·17; 0·38)
BMMC	5·58 ± 1·5	121 ± 15	0 (-0·31; 0·46)	0·055 (-0·05; 0·63)	0·33 (-0·80; 0·80)	0·22 (0; 1·89)
ADSC	5·87 ± 1·3	118 ± 21	0 (-0·7; 0·63)	0·079 (-0·7; 0·74)	-0·49 (-0·67; 117·7)	-0·34 (-0·55; 117·8)
Co-infusion	7·89 ± 2·2	142 ± 21	-0·54 (-0·62; 0·18)[a]	0·015 (-0·38; 0·41)	0·32 (-0·18; 0·70)	0·29 (-0·31; 127·94)
Forced expiratory volume in first second (FEV1)						
Control	1·1 ± 0·3	41 ± 7	0 (-0·03; 0·36)	0·1 (-0·01; -0·01)[a]	-0·2 (-0·08; 0·24)	-0·09 (-0·29; 0·28)
BMMC	1·03 ± 0·4	39 ± 6	0·3 (-1·03; 0·07)	0·1 (-0·22; 1·05)	0·07 (-0·06; 0·44)	0·9 (0·02; 0·22)[a]
ADSC	0·9 ± 0.1	38 ± 7	-0·4 (-0·18; 0·09)	0·04 (-0·15; 0·06)	-0·4 (-0·11; 0·22)	-0·5 (-0·14; -0·01)[a]
Co-infusion	1·01 ± 0·1	39 ± 6	-0·04 (-0·22; 0·04)	2·99 (-0·14; 0·14)	-0·2 (-0·14; 0·01)	-0·9 (-0·22; 0·01)
Residual volume (RV)						
Control	-	170 ± 104	6 (-11; 7)	-10 (-10; 10)	16 (5; 27)[a]	2 (-33; 40)
BMMC	-	204 ± 26	7.5 (-35; 48)	12.5 (-12; 32)	8 (-45; 46)	43 (-1; 97)
ADSC	-	201 ± 36	3 (-17; 25)	22 (-39; 34)	-28 (-41; 19)	-5 (-20; 10)
Co-infusion	-	233 ± 49	- 40 (-41; 17)	-1 (-46; 44)	9 (-21; 58)	-5.5 (-27; 29)
Residual volume/Total lung capacity (RV/TLC)						
Control	-	195 ± 33	0 (-14; 144)	-3 (-3; 3)	4.5 (4; 5)[a]	6 (-10; 123)
BMMC	-	186 ± 23	-2 (-28; 44)	-1 (-9; 24)	4 (-3; 26)	6 (-7; 61)
ADSC	-	199 ± 31	3 (-1; 11)	8 (-12; 158)	-13 (-158; 9)	1 (-12; 28)
Co-infusion	-	183 ± 41	-2 (-7; 6)	0.5 (-6; 7)	0 (-4; 6)	-2 (-2; 6)
Airway resistance (AR)						
Control	-	164 ± 47	-8 (-76; 35)	24 (24; 24)	-	1 (-138.57; 99)
BMMC	-	194 ± 80	-12 (-44; 31)	8,5 (-2; 55)	-66 (-76; 92)	-31 (-103; 86)

ADSC	-	187 ± 51	-2 (-30; 8)	46 (-28; 78)	-22 (-68; 93)	20 (-88; 84)
Co-infusion	-	151 ± 23	12 (8; 14)[a]	5 (-31; 41)	15 (-25; 41)	34 (22; 46)[a]
Diffusion lung capacity for carbon monoxide (DLCO)						
Control	-	47 ± 27	20 (5; 33)[a]	4 (4; 4)	-3 (-7; 0)	-5 (-25; 31)
BMMC	-	35 ± 26	15 (-1; 57)	3.5 (-14; 16)	1 (-15; 0)	17 (0; 43)[a]
ADSC	-	45 ± 29	8 (-10; 18)	3 (-4; 8)	-10 (-11; 1)	5 (-17; 15)
Co-infusion	-	35 ± 11	-10 (-13; 16)	8 (1; 15)[a]	-1 (-12; 7)	(-13; 57)
Alveolar volume (AV)						
Control	3·8 ± 1·1	64 ± 32	-8 (-11; -3)	7·5 (-2; 17)	-1 (-10; 20)	-2 (-4; 3)
BMMC	3·6 ± 1·2	67·2 ± 14	19 (9; 71·7)[a]	-3 (-10; 4)	4·5 (-5; 9)	8 (-16; 69·7)
ADSC	3·4 ± 0·8	67·8 ± 12	13·5 (0; 31)[a]	-7 (-11; 2)	7 (1; 14)[a]	25 (6; 27)[a]
Co-infusion	4·62 ± 1·5	84.2 ± 20	5 (-1; 13)	-4 (-5; 1)	0 (-7; 3)	-1(-5;11)
Diffusion lung capacity for carbon monoxide/Alveolar volume (DLCO/AV)						
Control	3 ± 1	56·6 ± 23	-7 (-11; 18)	6·5 (3- 10)	-6·5 (-8; -5)[a]	-5 (-13; 6)
BMMC	2·9 ± 1·3	57·7 ± 29	21 (4; 26)[a]	3 (3; 3)	-8 (-12; -1)	-6 (-24; 21)
ADSC	3.1 ± 1·4	64·6 ± 31	11·5 (-1; 56)	3·5 (-4; 36)	-9 (-42; -2)	7 (-7; 43)
Co-infusion	2·1 ± 0·4	43 ± 8·8	17 (-10; 20)	5 (-6; 14)	-9 (-16; 1)	12 (-14; 20)
Inspiratory capacity (IC)						
Control	-	77 ± 10	-15 (-15; -5)[a]	4 (-1; 9)	4 (-3; 7)	-5.5 (-28; 18)
BMMC	-	77 ± 16	3 (-1; 12)	-2 (-2; -2)[a]	-2 (-2; 12)	0 (-6; 1)
ADSC	-	71 ± 17	5·5 (1; 7)[a]	0 (-6; 2)	1 (0; 7)[a]	8 (2; 15)[a]
Co-infusion	-	80 ± 22	-1 (-19; 0)	-4 (-11; 5)	6 (-10; 17)	-4 (-21; 6)

Legend: ADSC, adipose-derived mesenchymal stromal cells; BMMC, bone marrow mononuclear cells. The data are expressed as mean ± SEM. Statistical comparisons were performed using one-way ANOVA. [a]$p < 0.05$, *vs*. Basal.