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Allogeneic mesenchymal stromal cell therapy on primary graft dysfunction after lung transplantation

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KEYWORDS:
Adipose tissue-derived mesenchymal stromal cells;
Allogeneic therapy;

BACKGROUND: Primary graft dysfunction (PGD) is common in lung transplantation affecting 15–30% of recipients. It represents a multifactorial injury to the transplanted lung within the first 72 hours after transplantation.

We aimed to investigate clinical safety and efficacy of allogeneic adipose tissue-derived stromal cells (ASCs), as an add-on therapy in patients undergoing double lung transplantation.

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Clinical trial;
Graft dysfunction;
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Stem cells

METHODS: Single center, double-blinded, investigator-initiated randomized phase I/II study with intravenous infusion of either ASCs or placebo within two hours after lung transplantation. A total of 31 patients were included and randomized 1:1:1 to either 200 million or 100 million ASCs, or placebo infusion.

The primary endpoint was difference in PGD grade 72 hours after transplantation between groups.
RESULTS: No significant differences in PGD were seen between the 3 groups 72 hours after lung transplantation (P=0.426). Combined ASC groups compared to placebo group did not show any difference in PGD 72 hours after transplantation (P=0.252). A reduced progression in PGD from day 1 to day 3 and day 2 to day 3 was observed between the ASC treated patients and patients in the placebo group (P=0.034 and P=0.034, respectively). There were no significant differences in number of serious adverse events or in secondary endpoints such as kidney function, lung function, or quality-of-life between groups.
CONCLUSIONS: Intravenous infusion of allogeneic ASCs in patients immediately after double lung transplantation was safe. The therapy did not show statistic difference in PGD between groups 72 hours after lung transplantation.
CLINICAL TRIAL REGISTRATION INFORMATION: EudraCT number 2019–004848-30 and NCT04714801.
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Background

Primary graft dysfunction (PGD) continues to be a common complication after lung transplantation affecting 15–30% of the recipients and leading to morbidity and mortality.[1,2] It represents a multifactorial injury to the transplanted lung and presents itself within the first 72 hours after the transplant procedure.[3,4] Several risk factors are associated with the development of PGD, mostly through inflammatory mechanisms.[5,6] The use of stem cell therapy has previously been suggested as a possible way to modulate this inflammation reducing the amount of PGD.[7]

Allogeneic adipose tissue-derived mesenchymal stromal cells (ASCs) have unique immunomodulatory traits, by which they can evade being recognized by the recipients immune system and have the potential to function as a immune suppressor in conditions where the recipient immune system is highly activated such as during organ transplantation.[8,9] The impact of this potential beneficial immune modulatory effect [10–12] has not, or only scantily, been investigated pre-clinically and clinically during lung transplantation. A study using allogeneic ASCs in a rat lung transplantation model has shown promising results.[13] The ASCs secrete different types of cytokines, which may transform alloreactive host immune cells into regulatory cells. Targeting particularly these immune cells with a mixture of cytokines after lung transplantation may reduce the incidence of PGD. However, the combination and amount of cytokines during the process of immune modulation is unknown.

Mesenchymal stromal cells can be obtained in high concentrations from adipose tissue, which is an attractive source for an allogeneic product.[14] ASCs are stable in cell cultures, have a high proliferative capacity, and a low extent of cellular senescence.[15]

The immunosuppressive potential of ASC is achieved by multiple complex interactions, the full picture of which is yet to be resolved. ASC employ both cell-cell contact-dependent immunoregulation, utilizing mechanisms such as surface receptors and receptor ligand interactions, and paracrine mechanisms. Through their secretome, ASC release a variety of bioactive molecules, including cytokines, growth factors, exosomes, and other soluble factors, which collectively contribute to their immunomodulatory effects.[10,16]

In this study, we aimed to investigate the safety and impact of intravenous infusion of allogeneic ASCs administrated within two hours after the transplant procedure on PGD 72 hours after lung transplantation.

Materials and methods

Study design and patient population

This study is a phase I/II, single center, double blinded randomized clinical trial with 1:1:1 assignment to either cell treatment with 200 million ASCs or 100 million ASCs, or placebo (saline) intravenous infusion within the first two hours after completion of the transplantation procedure as an add on therapy to standard immune suppressive treatment during lung transplantation.

The study protocol was approved by the Danish Ethical Committee (1911195) and the Danish Medicines Agency (2020070825) and complies with the Declaration of Helsinki. The study is registered in EudraCT (2019–004848-30) and ClinicalTrials.gov (NCT04714801).

Patients were consecutively enrolled from our center, when undergoing double lung transplantation. All patients had received oral and written information about

Table 1 Inclusion and Exclusion Criteria for Patients in this Trial

Inclusion Criteria
• Male or female lung transplant recipients 18–70 years of age undergoing primary double (including size reduction) lung transplantation
• Patient willing and capable of giving written informed consent for study participation and anticipated to be able to participate in the study for 3 months
Exclusion criteria
• Recipients of multi-organ transplant, and or previously transplanted with any solid organ, including previous lung transplantation
• Patients scheduled for single lung transplantation
• Patients in need of acute transplantation e.g., patients on urgent call for transplantation and patients on respirator or on extra corporal membrane oxygenation (ECMO) treatment at time of transplantation
• Patients with a planned ECMO treatment when the lung is transplanted
• Patients during lung transplantation needing unexpected ECMO support
• Patients that needs cross-match prior to transplantation
• Donor lung cold ischemic time without oxygenation > 12 h
• Patients with platelet count < 50,000/mm3 at the evaluation prior to transplantation
• Patients unlikely to comply with the study requirements
• Patients with any past (within 3–5 years) or present malignancy (other than excised basal cell carcinoma)
• Females capable of becoming pregnant must have a negative pregnancy test prior to transplantation and must use contraceptives for 2 months following the given cell therapy

the study and signed a written informed consent prior to inclusion. No human leucocyte antigen (HLA) matching was performed between ASC donor, recipient, or graft. Matching between lung donor and recipient followed standard procedure.

The patients were followed clinically for 3 months in this study.

Inclusion and exclusion criteria are listed in Table 1.

Cell manufacturing

The ASCs were produced in an approved Good Manufacturing Practice (GMP) facility in Cardiology Stem Cell Center (CSCC) at Rigshospitalet, University Hospital of Copenhagen, Denmark (manufacturing authorization 38940, tissue establishment authorization DK261985) The manufacturing procedure follows the European Union guidelines for Good Manufacturing Practice of Medicinal Products for Human Use (certificate of GMP compliance no. DK IMP 130620).

The ASC donors were tested for HIV, hepatitis B and C, syphilis and HTLV I/II by serum analysis prior to liposuction and on the day of donation. Donor tissue typing (low HLA I and II genotyping) was performed.

In local anesthesia, liposuction was performed from abdominal adipose tissue of a healthy donor. Between 100–150 mL lipoaspirate was obtained from each donor, followed by expansion in growth medium supplemented with human platelet lysate (Sexton Biotechnologies) in automated closed bioreactor systems (Quantum Cell Expansion System, Terumo BCT), as previously described.[17–19] The final cell product was used after two passages. Harvested ASCs were cryopreserved in CellSeal vials (Sexton Biotechnologies) (100 million cells in 5 mL) in CryoStor CS10 (BioLife Solutions) and stored below −180 °C in nitrogen dry storage until clinical use. The presence of mycoplasma was tested from all bioreactor expansions immediately prior to cell harvest and the presence of bacteria, fungi and endotoxins was tested on the final product, immediately prior to cryopreservation. Batch release criteria were sterility, endotoxin < 70IU/mL, viability (> 80%), identity and purity (CD90, CD105, CD73 > 80% and CD45 < 3% and HLA-DR < 5%).[19] Three ASC donors were used to produce the vials for this trial. Each patient in the active therapy arm was treated with ASCs obtained from one donor only.

Cell delivery

The ASCs was thawed at 37 °C and prepared for infusion immediately before treatment.

The thawed cells were diluted in 100 mL of isotonic saline, which was infused slowly through a cubital vein within 30 minutes, thereby reaching the small vessels in the lungs where most of the infused ASCs will be caught in the lung tissue.[20] No simultaneous infusions of any drugs were administered in the same catheter during the 30 minutes. For practical reasons, the treatment was performed in the intensive care unit as quickly as possible after restoration of blood supply to the grafts. The same person from CSCC prepared the infusion bag and performed the cell infusion in all included patients.

Immunosuppressive treatment

The patients received standard immunosuppressive treatment as follows: Pre-procedure induction with tacrolimus 0.1mg/kg.

Day 0 (day of lung transplantation): intravenous 1000 mg methylprednisolone before reperfusion, i.e., restoration of blood flow of the transplanted allograft.

Following the procedure, in the intensive care unit: intravenous methylprednisolone 125 mg every 12 hours counting from the last dose in the operation room, altogether 3 doses over 36 hours in conjunction with mycophenolic acid 1 g x 2 and tacrolimus aiming at trough levels between 10–14 ng/mL.

From day 2: Prednisolone initiated at 1mg/kg/day and tapered to 0.2mg/kg/day over 10 days.

Randomization and masking

Patients were randomized in blocks of six using a web program.[21]

CSCC was responsible for the randomization code and for preparing the cell product in the infusion bag, to assure blinding of the treatment for the clinical team. It was not possible to see whether it was 200 or 100 million ASCs or placebo (saline) in the prepared infusion bag.

Outcomes

The *primary endpoint* was difference in PGD 72 hours after lung transplantation between groups.

The *secondary endpoints* were differences in kidney function, lung function, change in biomarkers and quality of life.

Safety data for all groups were collected and difference in serious adverse events (SAE) at 3 months follow-up was analysed.

PGD was defined according to the International Society for Heart and Lung Transplantation (ISHLT) as pulmonary infiltrates and hypoxemia occurring in the first 72 hours after transplantation.[3] PGD was graded every 24 hours during the first 72 hours after transplantation. Time started at reperfusion of the second lung.

PGD was analysed and graded by two independent consultants with expertise in lung transplantations and blinded to the patient's treatment status. If there was disagreement in PGD, consensus had to be reached.

Olink analysis

At baseline, day 3, day 7, day 14, day 28 and week 12, plasma EDTA samples were drawn and stored at −80 °C. Samples were analyzed by BioXpedia (Aarhus, Denmark) using the Olink Target 96 Inflammation panel. Variables with normalized protein expression (NPX) values below limit of detection (LOD) in more than 44% of cases were excluded (25 proteins). The remaining variables had less than 13.6% NPX < LOD. The distribution and cut-off are illustrated in supplemental Figure E1. Data analysis was performed in R [22] and RStudio [23] using the Olink Analyze package (version 3.4.1) to conduct principal component analysis, heatmaps and linear mixed effect models. For linear mixed effect models, the data was scaled to baseline values. Significant differentially expressed proteins from baseline to day 3 were identified by olink_ttest (Welch 2-sample t-test, Benjamini & Hochberg (BH)-adjusted p-values < 0.05) and illustrated using the VennDiagram package.[24] By addressing the proteins as genes, Gene Ontology Enrichment Analysis was used to detect significant "Biological Process" terms, using BH-adjusted p-values < 0.01 in clusterProfiler [25] against the org.Hs.eg.db human annotation package. The results were plotted using DOSE.[26] All included NPX and baseline-scaled data are depicted as spaghetti plots in supplemental Figures E2 and E3.

Statistical analysis

Statistical analysis was performed using SPSS version 29 (SPSS Inc., Chicago, Illinois). Continuous variables are presented as mean ± standard deviation and categorical variables are presented as numbers and percentages. Categorical data are compared using Fisher's exact or Chi-square test as appropriate. Analysis of variances (Anova) is used to compare more than two groups for normal data distribution. A two-sided P-value of < 0.05 is considered statistically significant. It was predefined in the protocol that the ASC groups would be analysed alone and combined against the placebo group.

Results

Thirty-one patients were included from December 2020 to April 2023. During transplantation, one patient developed an unexpected need for extra corporal membrane oxygenation and thus was excluded before ASC/placebo treatment according to the in- and exclusion criteria (Figure 1).

Patient characteristics are presented in Table 2.

Ten women and 20 men were treated with 200 million ASCs (n=10), 100 million ASCs (n=10) or saline infusion (n=10). No statistically significant differences in major baseline characteristics were observed between the three groups except in forced vital capacity and quality of life activity score.

One patient experienced hypoxic cardiac arrest and died later due to cerebral anoxia on day 7 after lung transplantation.

Operative characteristics

There were no significant differences between the three groups in the time used to perform the lung transplantation, in ischemic time for the lungs to be transplanted, in use of red blood cells, platelets or fresh frozen plasma given per- or post-operatively (Table 2). One patient required post-operative dialysis. No ex-vivo lung perfusion (EVLP) was done in the placebo group.

Primary graft dysfunction

The distribution of the PGD grade in the three groups is shown in Table 3. There were no significant differences between the groups 72 hours after lung transplantation (P=0.426). Neither was there any significant difference when the ASC groups were combined and compared to placebo (P=0.252).

Interestingly, there was a significant difference between the ASC groups compared to placebo in the PGD change from day 1 to day 3 (P=0.034) and from day 2 to day 3 (P=0.034) in favour of cell therapy (Figure 2).

PaO2/FIO2 ratio at 72 hours was 48 ± 25, 38 ± 21 and 50 ± 18 in the group treated with 200 million ASC, 100 million ASC and placebo, respectively. There was no

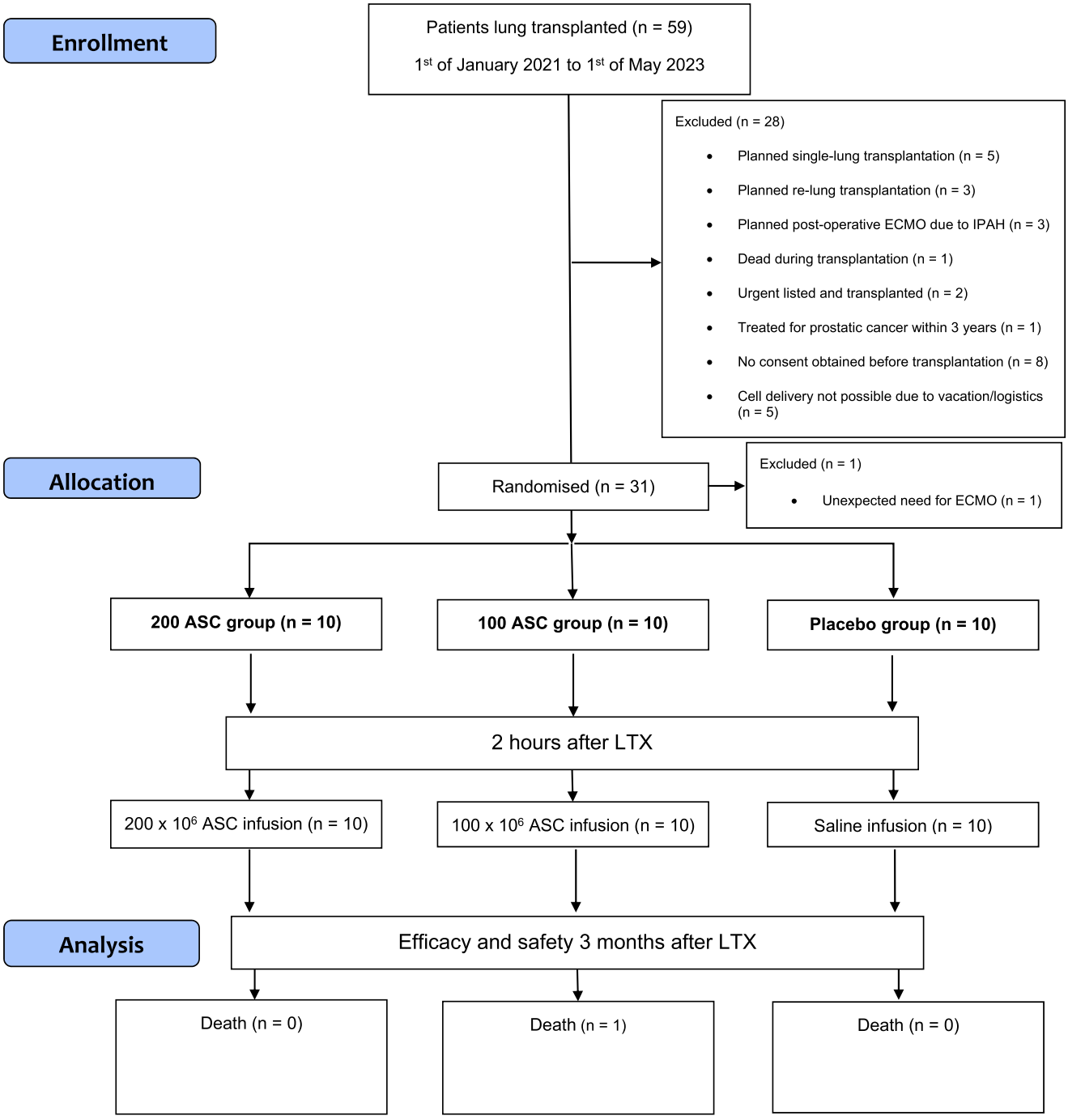

Figure 1 Overview of the study.

statistical difference between the three groups (P=0.402) or between treated and placebo group (43 ± 23 and 50 ± 18, P=0.408).

Secondary endpoints: Kidney function, leucocytes, C-reactive protein and lung function

Measured GFR by Chrome-EDTA clearance was performed at baseline and 3 months after lung transplantation. Creatinine was also measured at the same time points. No significant differences between the groups were observed (Table 4).

There were no changes in leucocytes or C-reactive protein from baseline to 3 months follow-up between the groups (P > 0.05) (Table 4).

The lung function measured 3 months after lung transplantation was not different between the three groups (P > 0.05) (Table 5).

Quality of life

Self-reported quality of life measured by EQ-5D-5L was not different in change from baseline to 3 months follow-up between groups in the 5 dimensions: mobility (P=0.104),

Table 2 Baseline Characteristics of Patients Undergoing Lung Transplantation and The Donor Lungs

Parameter	ASC, 200×10^6 (n=10)	ASC, 100×10^6 (n=10)	Placebo (n=10)	P-value
Baseline profile				
Age (years)	55.5 ± 6.8	59.6 ± 5.6	55.6 ± 6.2	0.262
Gender (Male)	6 (60.0)	7 (70.0)	7 (70.0)	0.861
BMI (kg/m^2)	24.4 ± 3.5	24.7 ± 4.1	23.1 ± 4.7	0.655
Systolic blood pressure (mmHg)	137 ± 18	133 ± 19	133 ± 24	0.854
Diastolic blood pressure (mmHg)	85 ± 13	81 ± 15	85 ± 15	0.834
Heart rate (bpm)	88 ± 21	85 ± 17	91 ± 16	0.715
Saturation (%)	97 ± 2	96 ± 3	97 ± 2	0.364
Lung characteristics				
COPD	3 (30.0)	2 (20.0)	3 (30.0)	0.843
IPF	6 (60.0)	7 (60.0)	6 (60.0)	0.866
PAH	1 (10.0)	0 (00.0)	0 (00.0)	0.355
α1-antitrysin deficiency	0 (00.0)	2 (20.0)	1 (10.0)	0.329
Bronchiectasis	1 (10.0)	0 (00.0)	0 (00.0)	0.355
Sarcoidosis	0 (00.0)	1 (10.0)	1 (10.0)	0.585
SPH	1 (10.0)	0 (00.0)	2 (20.0)	0.329
Smoking				
never	3 (30.0)	1 (10.0)	2 (20.0)	0.543
previous	7 (70.0)	8 (80.0)	8 (80.0)	
current	0 (00.0)	1 (10.0)	0 (00.0)	
Lung function				
FEV1 (L)	1.7 ± 0.9	1.5 ± 0.9	1.0 ± 0.7	0.226
Predicted FEV1 (%)	53.6 ± 26.2	45.8 ± 24.6	33.8 ± 22.8	0.231
FVC (L)	2.5 ± 0.8	2.3 ± 0.7	1.6 ± 0.7	0.047
Predicted FVC (%)	65.2 ± 21.1	56.0 ± 16.9	41.9 ± 16.0	0.033
TLC (L)	5.3 ± 2.3	6.5 ± 3.2	5.5 ± 3.3	0.665
Predicted TLC (%)	86.4 ± 35.9	97.9 ± 45.5	90.4 ± 52.3	0.852
FRC (L)	3.61 ± 2.2	6.0 ± 5.7	4.3 ± 3.2	0.421
Predicted FRC (%)	113.0 ± 66.3	143.0 ± 91.0	134.6 ± 96.5	0.731
RC (L)	2.7 ± 2.3	4.0 ± 3.2	3.7 ± 3.1	0.615
Predicted RC (%)	132.61 ± 104.88	174.4 ± 136.8	180.9 ± 147.7	0.681
DLCO	2.6 ± 1.0	2.3 ± 0.6	2.2 ± 1.0	0.605
Predicted DLCO (%)	28.15 ± 10.2	24.1 ± 6.7	23.6 ± 9.5	0.497
EQ–5D-5L				
Mobility score	2.8 ± 0.8	3.1 ± 1.1	3.9 ± 0.4	0.097
Self-care score	2.3 ± 1.0	2.5 ± 1.2	3.4 ± 0.8	0.134
Activity score	2.8 ± 1.0	4.0 ± 0.5	4.4 ± 0.5	0.002
Pain/discomfort score	2.2 ± 1.0	2.9 ± 1.0	3.0 ± 1.0	0.294
Anxiety/Depression score	1.8 ± 0.4	1.8 ± 0.9	2.6 ± 1.1	0.184
Scale score	41.4 ± 25.0	27.38 ± 13.1	21.0 ± 6.2	0.084
Biochemical profile				
Haemoglobin (mmol/L)	8.77 ± 1. 7	8.7 ± 0.8	8.8 ± 0.9	0.996
Leucocytes (10^9/L)	10.2 ± 3.7	10.2 ± 2.7	10.2 ± 2.8	0.997
Platelets (10^9/L)	332.9 ± 126.9	267.5 ± 72.8	287.4 ± 57.2	0.272
Creatinine (µmol/L)	72.4 ± 12.1	78.3 ± 14.4	63.6 ± 14.9	0.075
ALAT (µkat/L)	22.89 ± 8.8	24.8 ± 13.39	35.9 ± 24.0	0.206
CRP (mg/L)	7.5 ± 13.0	9.1 ± 8.6	3.0 ± 3.4	0.322
Uric acid (mmol/L)	4.5 ± 1.1	5.2 ± 1.8	4.6 ± 1.1	0.546
Chrome-EDTA-clearance	96.0 ± 9.1	98.4 ± 24.6	103.88 ± 23.54	0.740
Characteristics of donor lung				
Age (years)	46.7 ± 15.0	47.8 ± 16.5	35.9 ± 17.9	0.223
Gender (Male)	6 (60.0)	5 (50.0)	6 (60.0)	0.873
Height (cm)	171.9 ± 7.0	176.2 ± 8.5	171.1 ± 7.3	0.288
Weight (kg)	73.7 ± 13.4	81.8 ± 16.1	69.7 ± 13.9	0.183
Smoking				
never	5 (50.0)	5 (50.0)	6 (60.0)	0.939
previous	2 (20.0)	1 (10.0)	2 (20.0)	
current	3 (30.0)	3 (30.0)	2 (20.0)	

(*continued on next page*)

Table 2 (*Continued*)

Parameter	ASC, 200×10^6 (n=10)	ASC, 100×10^6 (n=10)	Placebo (n=10)	P-value
Alcohol consumption				
no	7 (70.0)	6 (60.0)	7 (70.0)	0.267
yes	3 (30.0)	3 (30.0)	0 (0.0)	
previous	0 (0.0)	0 (0.0)	1 (10.0)	
Days on mechanical ventilation	3.1 ± 1.7	3.9 ± 2.6	3.5 ± 3.1	0.782
Lung transplantation				
Operative time (min)	404 ± 49	453 ± 98	406 ± 84	0.313
Ischemic time for the first lung (min)	352 ± 128	336 ± 170	228 ± 65	0.081
Ischemic time for the second lung (min)	453 ± 131	431 ± 164	325 ± 86	0.082
EVLP time (min)	41 ± 86.6	66.7 ± 109.2	0 ± 0	0.193
PaO2/FiO2 (kPa)	47.9 ± 24.9	37.5 ± 20.6	49.7 ± 18.3	0.402
Time to extubation (min)	3187 ± 7632	1082 ± 795	2136 ± 4685	0.667
ICU stay (hours)	115 ± 132	118 ± 49	119 ± 98	0.996
Intraoperative use of:				
red blood cells	7 (70.0)	3 (30.0)	4 (40.0)	0.175
platelets	7 (70.0)	4 (40.0)	3 (30.0)	0.175
fresh frozen plasma	6 (60.0)	4 (40.0)	1 (10.0)	0.065
cryoprecipitate	1 (10.0)	0 (00.0)	1 (10.0)	0.585
fibrinogen	1 (10.0)	0 (00.0)	0 (00.0)	0.355
novo–7	0 (00.0)	0 (00.0)	0 (00.0)	1.000
Perioperative dialysis	0 (00.0)	0 (00.0)	0 (00.0)	1.000
Postoperative use of:				
red blood cells	4 (40.0)	5 (50.0)	5 (50.0)	0.875
platelets	4 (40.0)	3 (30.0)	4 (40.0)	0.866
fresh frozen plasma	4 (40.0)	3 (30.0)	3 (30.0)	0.861
cryoprecipitate	0 (00.0)	0 (00.0)	0 (00.0)	1.000
fibrinogen	1 (10.0)	0 (00.0)	0 (00.0)	0.355
novo–7	0 (00.0)	0 (00.0)	0 (00.0)	1.000
Postoperative dialysis	1 (10.0)	0 (00.0)	0 (00.0)	0.435
Postoperative infection	2 (20.0)	1 (10.0)	1 (10.0)	0.308

Values are mean ± SD or n (%) ALAT = Alanine aminotransferase, BMI = Body mass index, BPM = Beats per min, COPD = Chronic obstructive pulmonary disease, CRP = C-reactive protein, DLCO = Diffusing capacity of the lungs for carbon monoxide, EVLP = Ex vivo lung perfusion, FEV1 = Forced expiratory volume in 1 s, FRC = forced residual volume, FVC = Forced vital capacity, IPF = Interstitial pulmonary fibrosis, ICU = Intensive care unit, PAH = Pulmonary arterial hypertension, RC = Residual capacity, TLC = Total lung capacity, SPH = Secondary pulmonary hypertension.

Table 3 Primary Graft Dysfunction 72 h After Lung Transplantation

Primary Graft Dysfunction Grade	ASC, 200×10^6 (n=10)	ASC, 100×10^6 (n=10)	Placebo (n=10)	P-value
0	4 (40.0)	6 (60.0)	3 (30.0)	0.426
1	4 (40.0)	2 (20.0)	2(20.0)	
2	0 (0.0)	1 (10.0)	3 (30.0)	
3	2 (20.0)	1 (10.0)	2 (20.0)	

Values are n (%)

selfcare (P=0.091), usual activities (P=0.298), pain/discomfort (P=0.466) or anxiety/depression (P=0.855) measured on a 5-level score: no problems, slight problems, moderate problems, severe problems or extreme problems.[27]

The patients reported how good/bad their day was on a scale from 0–100 at baseline and 3 months after lung transplantation. In the group treated with 200 million ASCs, the patients reported a value of 41 ± 25 at baseline and 73 ± 10 at 3 months follow-up. In the group treated with 100 million ASCs, the patients reported 27 ± 13 and 71 ± 15 at baseline and 3 months follow-up, respectively. In the placebo group, the patients reported a value of 21 ± 6 and 73 ± 16 at baseline and 3 months follow-up, respectively. There were no statistically significant differences between groups (P=0.641).

Biomarkers

Principal component analysis (PCA) was performed on all samples using two components to reveal temporal changes (Figure 3A). From the plot, it is evident how the greatest difference is between baseline and day 3 samples, with subsequent samples gradually returning towards baseline. The analysis explained 43.27% of the total variation. Unsupervised clustering of samples in the heatmap did not reveal distinct clustering regarding treatment. However, a closer relation to the time point was observed (Figure 3B).

To address differences between ASC and placebo groups, the significant differences are presented in Figure 3C. Overall, the changes were small. Relative to baseline,

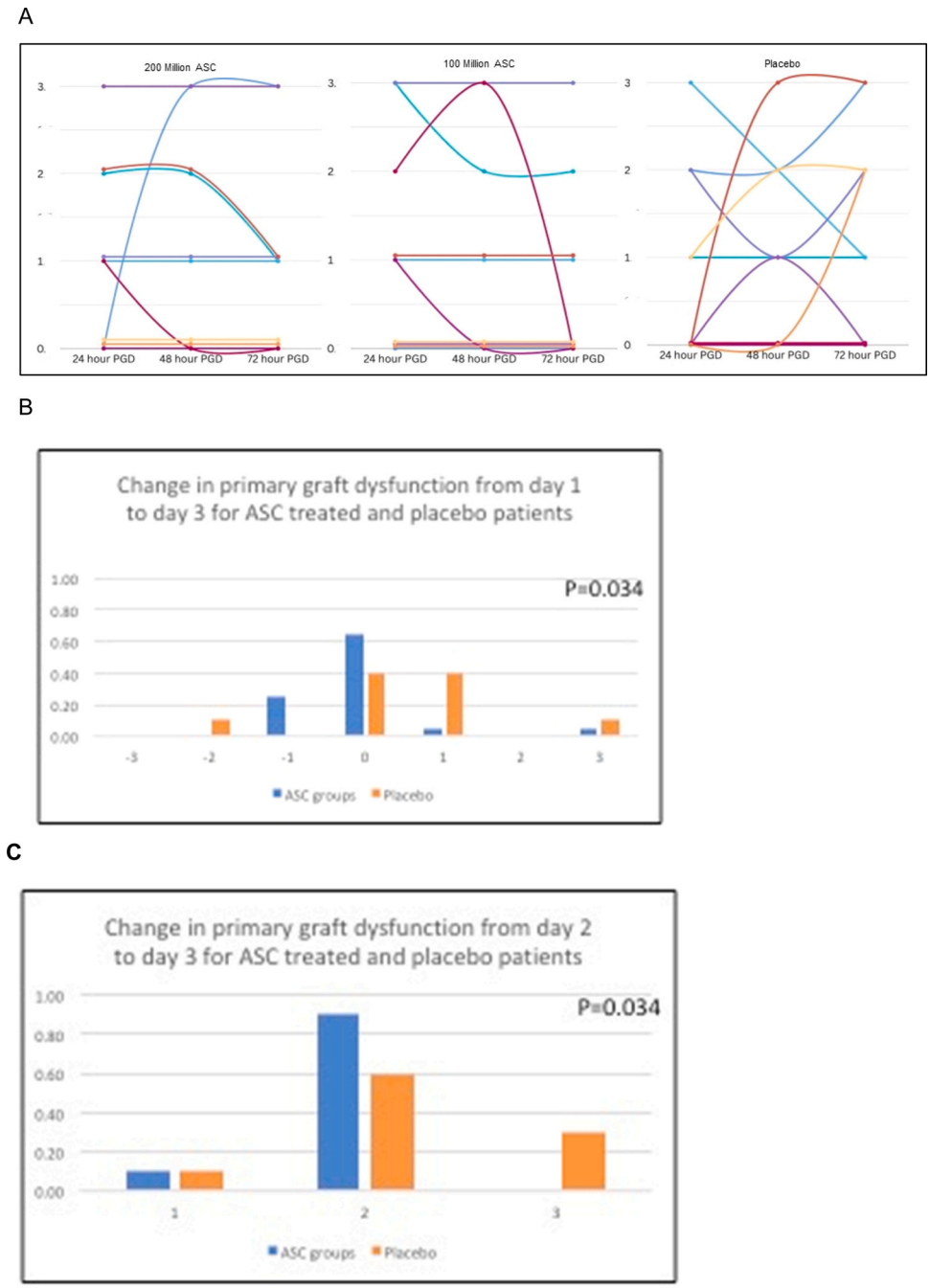

Figure 2 (A) Primary graft dysfunction (PGD) at 24, 48 and 72 h after lung transplantation and difference in PGD (B) from day 1 to day 3 and (C) from day 2 to day 3 in patients treated with adipose tissue-derived stromal cells (ASCs) and placebo group.

the placebo group displayed a higher increase in fibroblast growth factor 23 (FGF-23). When assessing differences between doses, the expression of leukemia inhibitory factor receptor (LIF-R) was slightly lower in the patients receiving a high dose of ASCs (High dose – placebo, $P < 0.0001$; High dose – low dose, P=0.0006), especially at day 14 (Figure 3D). Albeit small, the reduction in FGF-23 appeared to be dependent on dose (High dose – placebo, $P < 0.0001$; Low dose – placebo, P=0.0152). All data included in the analysis are illustrated as spaghetti plots in supplemental Figure E2 and E3, providing visual insights into the individual variability and trends over time.

As the largest difference in markers in the PCA was between baseline and day 3, we further investigated the changes between these time points. Of the 53 significant variables, the majority of differentially expressed proteins were common between ASC and placebo group (Figure 4). A subset of 14 proteins were unique to the ASC group, and only two unique in the placebo group. While Gene Ontology Enrichment Analysis displayed a shared involvement of broad biologic process terms related to the common proteins, more terms involving B cell activation and proliferation was enriched in the proteins unique to the ASC group. Likewise, two terms associated with macrophages

Table 4 Chrome-EDTA Clearance, Creatinine, Leucocytes and C-reactive Protein (CRP) Measured in the Three Groups at Baseline and 3 Months After Lung Transplantation

	ASC, 200×10^6 (n=10)		ASC, 100×10^6 (n=10)		Placebo Group (n=10)		P-value for Difference from Baseline to 3 Months FU Between Groups
	Baseline	3 months FU	Baseline	3 months FU	Baseline	3 months FU	
Chrome-EDTA (mL/min)	96.0 ± 9.1	66.2 ± 24.9	98.4 ± 24.6	65.4 ± 17.0	103.9 ± 23.5	66.6 ± 16.9	0.440
Creatinine (µmol/L)	72.4 ± 12.1	84.6 ± 18.3	78.3 ± 14.4	103.6 ± 25.6	63.6 ± 14.9	83.6 ± 18.7	0.431
Leucocytes (10^9/L)	10.2 ± 3.7	6.3 ± 2.3	10.2 ± 2.7	6.6 ± 3.2	10.2 ± 2.8	6.2 ± 2.4	0.745
CRP (mg/L)	7.5 ± 13.0	18.2 ± 35.7	9.1 ± 8.6	13.1 ± 15.4	3.0 ± 3.4	2.6 ± 2.6	0.634

Values are mean ± SD
CRP = C-reactive protein, FU = Follow-up

Table 5 Pulmonary Function at Baseline and 3 Months After Lung Transplantation

	ASC, 200×10^6 (n=10)		ASC, 100×10^6 (n=10)		Placebo Group (n=10)		P-value Between Groups at 3 Months FU
	Baseline	3 Months FU	Baseline	3 Months FU	Baseline	3 Months FU	
FEV1 (L)	1.7 ± 0.9	2.2 ± 1.0	1.5 ± 0.9	2.4 ± 1.2	1.0 ± 0.7	2.3 ± 0.7	0.857
FVC (L)	2.5 ± 0.8	2.7 ± 0.9	2.3 ± 0.7	3.7 ± 1.4	1.6 ± 0.7	2.7 ± 0.6	0.066
TLC (L)	5.3 ± 2.3	4.4 ± 1.3	6.5 ± 3.2	5.9 ± 1.7	5.5 ± 3.3	4.3 ± 1.3	0.061
FRC (L)	3.61 ± 2.2	2.7 ± 0.9	6.0 ± 5.7	3.4 ± 1.3	4.3 ± 3.2	2.6 ± 1.1	0.308
RC (L)	2.7 ± 2.3	1.8 ± 0.7	4.0 ± 3.2	2.1 ± 0.9	3.7 ± 3.1	1.7 ± 0.8	0.608
DLCO	2.6 ± 1.0	4.7 ± 1.4	2.3 ± 0.6	5.7 ± 2.0	2.2 ± 1.0	4.6 ± 1.0	0.289

Values are mean ± SD
DLCO = Diffusing capacity of the lungs for carbon monoxide, FEV1 = Forced expiratory volume in 1 s, FRC = forced residual volume, FU = Follow-up, FVC = Forced vital capacity, RC = Residual capacity, TLC = Total lung capacity.

were among the 10 most represented terms. No significant terms were identified for the proteins unique to the placebo group.

Safety data

Six patients had a SAE in the 200 million ASC group during the 3 months follow-up, while four patients in the 100 million ASC group and five patients in the placebo group had a SAE, respectively (Table 6). No significant differences were observed between the 3 groups (P=0.670). There was no difference between the ASC treated and placebo group (P=1.00).

There were no differences in the number of SAEs between the three groups (P=0.724) or between ASC treated and placebo groups (P=0.905) (Table 6). There were no adverse events suspected related to the cell therapy.

Discussion

This is the first clinical trial using allogeneic ASCs in human double lung transplants to investigate the safety and efficacy as an add-on therapy to avoid PGD at 72 hours. Obstacles experienced during the era of autologous cell therapy have now been reduced by the introduction of allogeneic cell therapy showing its safety in recent published trials.[28–30]

The results from this initial experience show that intravenous infusion is safe, logistical feasible in a sub-acute setting and that PGD progression was reduced in the ASC treated groups compared to the placebo group from day 1 to day 3 and day 2 to day 3. Interobserver correlation coefficient and 95% confidence interval based on a consistency, two-way random-effects model was 0.90 (0.83–0.94), indicating a good reliability of the performed PGD values. Two studies have used the current allogeneic ASC product to treat patients with dry eye disease (Sjögrens Syndrome) and head and neck cancer patients with radiation induced xerostomia, which indicated that the beneficial effect of ASCs may be related to modulation of the immune system.[31,32]

In this trial, we chose the lower ASC dose based on our previous experience in heart failure patients and decided to add a larger dose due to the larger organ involved.[28–30]

Two patients in the high dose ASC group and three patients in the low dose ASC group received EVLP lungs. No EVLP was done in the placebo group, which may have had an influence on our PGD results, as EVLP is used for marginal donor lungs in our center. Stratified randomisation would have avoided unequal distribution.

There were no significant differences in kidney function, inflammatory parameters, lung function or in quality-of-life scores at 3 months follow-up.

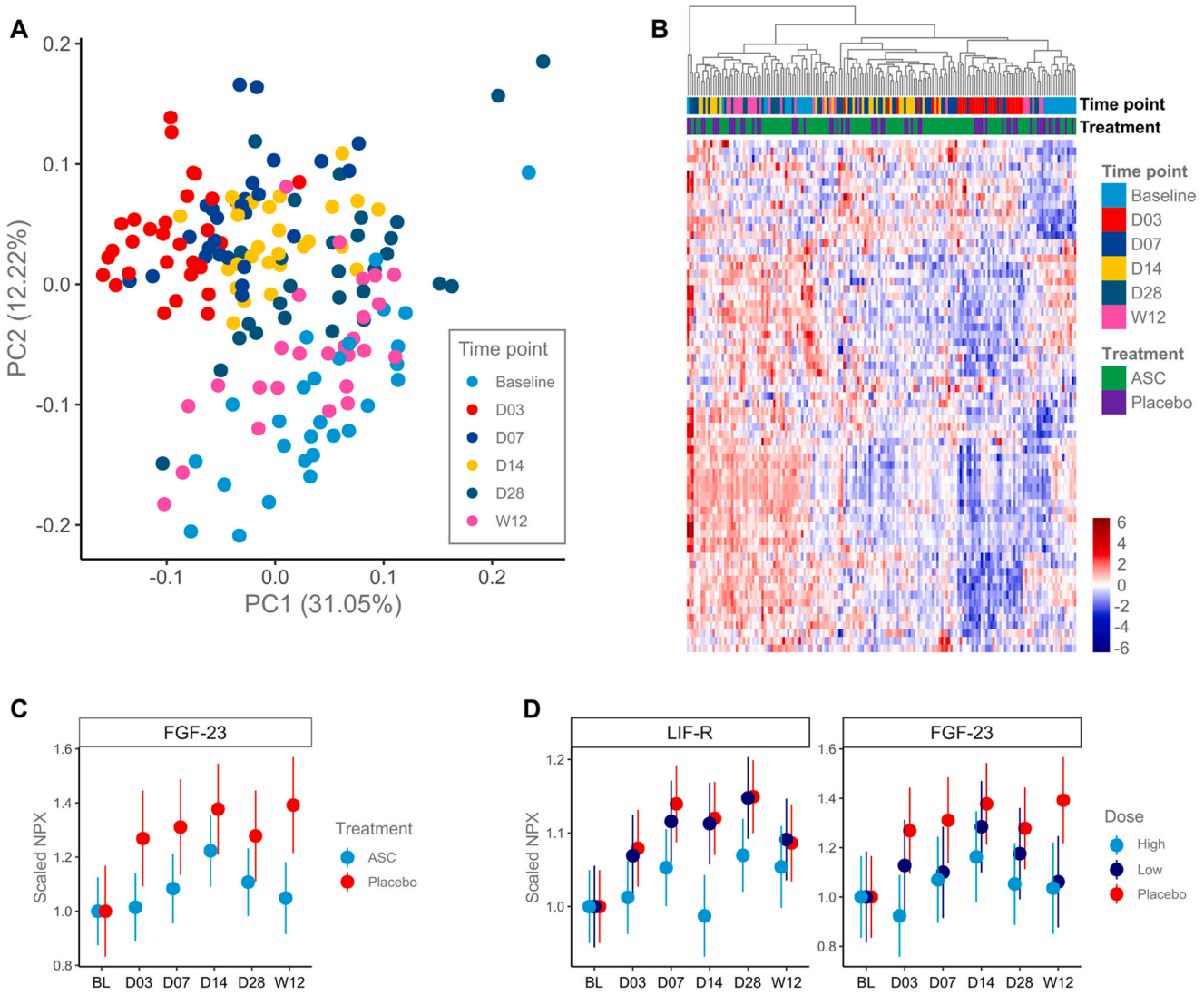

Figure 3 Circulatory protein markers of inflammation. (A) Principal component analysis of samples color-coded by time point. (B) Heatmap of analyzed proteins, grouped by unsupervised clustering. Colored by Time point and Treatment. (C) Significant differences in fibroblast growth factor (FGF-23) by linear mixed effect model between ASC-treated and placebo group, and (D) between doses.

Importantly, the safety measured as the absence of SAEs were identical between the groups. There were no acute cellular rejections registered in patients treated with 100 million ASCs while 7 patients from the 200 million ASC group and 3 patients in the placebo group were registered as having an acute cellular rejection. This must be considered in future trials.

Although it is a small clinical trial with three groups and PGD as endpoint, which is graded semi-objectively, the results indicate an effect of ASC treatment. However, an effect beyond 3 months follow-up may also be of interest. To detect a minimum effect of 10% in PGD and with a rate of 7.5% under null hypothesis with 5% alpha value, 80% power and 1:1:1 randomisation, a sample size of 115 would be needed in each group. Under the same conditions with only one active group, the sample size would have to be 266 patients in total.

It can be discussed whether ASC treatment within two hours after the procedure was optimal. Circulatory stability before infusion of cells is warranted as well as avoiding bleeding and leakage. With the intention to deliver the cells as soon as possible to the donor lungs, a two-hour window after completion of lung transplantation, was a pragmatic compromise in a real-world setting. One could consider the possibility of treating the donor lungs even before implantation as an option, e.g., with the help of EVLP or direct instillment on the back table. In this setting, we aimed to avoid factors influencing PGD, such as extra corporal membrane oxygenation (ECMO) etc.

Olink analysis of inflammatory markers revealed very small differences in the investigated circulating proteome. This finding is consistent with previous observations in patients with non-ischemic heart failure treated with ASCs [33] and suggests that the immune modulatory effect of ASC may not be reflected systemically by soluble markers. We choose the Olink inflammation panel because of our hypothesis about the immune modulatory properties of the cell product.

The placebo group exhibited a more pronounced increase in FGF-23 compared to the ASC group, and this

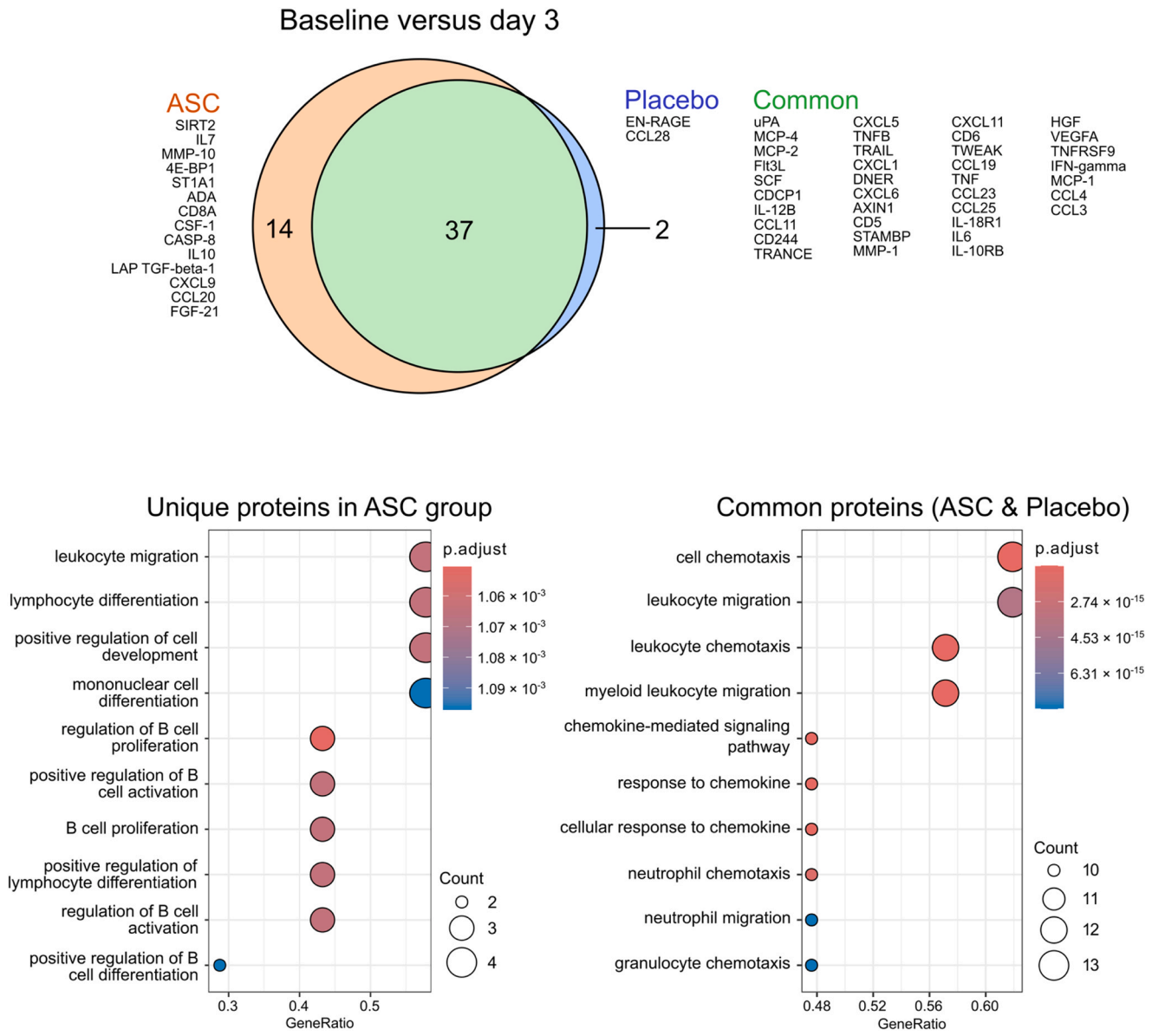

Figure 4 Differentially expressed proteins between baseline and day 3. Of 53 proteins, 14 were unique to the ASC group, 2 to the placebo group, and 37 common between groups. The top 10 significant "biological process" terms from Gene Ontology Enrichment Analysis for the ASC group and common proteins. No significant terms ($P < 0.01$) were identified for the placebo group.

elevation demonstrated a dose-dependent relationship. While increased inflammation may result in elevated FGF-23 production, our findings suggest a nuanced relationship, as no concomitant elevation in other markers indicative of a higher inflammatory state was observed.[34] The only other factor that differed significantly, LIF-R, did so to an even lesser extent and only in the patients receiving a high dose of ASCs. Due to the pleiotropic nature of LIF-R, caution should be advised when drawing conclusions about the subtle differences observed and due to multiple testing.

Differences in circulatory markers between baseline and day 3 were observed. Many proteins were shared between the groups, leading to biological process terms primarily associated with the immune system. This result was not surprising, as the Olink targeted panel specifically focused on inflammatory markers. Of particular interest was the presence of unique proteins in the ASC-group associated with B cells. This finding was intriguing, especially in the light of previous observations of transient alloantibodies in related studies.[28] Recent literature had suggested that mesenchymal stromal cell (MSC) might induce a regulatory B cell phenotype as part of their immunomodulatory mode of action and that increased regulatory B cells is a marker of clinical response to MSC in systemic sclerosis.[35,36] However, it remained to be determined whether the altered profile in the ASC group is indicative of either process. Additionally, terms involving macrophages were more prevalent in the ASC group. This observation was interesting, as the interaction with macrophages had been suggested to be central for MSC-based therapy.[37,38]

Our study highlights the complexity of the effect of ASC on the inflammatory response. While FGF-23 and to some extent LIF-R was lower in the patients receiving ASC therapy, the absence of corresponding changes in other

Table 6 Serious Adverse Events After 3 Months Follow-up

Serious Adverse Events	ASC, 200×10^6 (n=10)	ASC, 100×10^6 (n=10)	Placebo Group (n=10)	P-value
Yes	6 (60.0)	4 (40.0)	5 (50.0)	0.670
No	4 (40.0)	6 (60.0)	5 (50.0)	
Number of Serious Adverse Events	**ASC, 200×10^6 (n=10)**	**ASC, 100×10^6 (n=10)**	**Placebo Group (n=10)**	**P-value**
0	4 (40.0)	6 (60.0)	5 (50.0)	0.724
1	2 (20.0)	3 (30.0)	3 (30.0)	
2	3 (30.0)	1 (10.0)	2 (20.0)	
3	0 (0.0)	0 (0.0)	0 (0.0)	
4	1 (10.0)	0 (0.0)	0 (0.0)	
Event	**ASC, 200×10^6 (n=10)**	**ASC, 100×10^6 (n=10)**	**Placebo (n=10)**	**P-value**
Death	0 (0.0)	1 (10.0)	0 (0.0)	0.355
Acute cellular rejection	7 (70.0)	0 (0.0)	3 (30.0)	0.004
Pneumonia				
bacterial	2 (20.0)	7 (70.0)	3 (30.0)	0.054
fungal	1 (10.0)	1 (10.0)	0 (0.0)	0.585
viral	0 (0.0)	2 (20.0)	2 (20.0)	0.315
Recurrent pleural effusion	1 (10.0)	1 (10.0)	1 (10.0)	1.000
Pulmonary embolism	0 (0.0)	2 (20.0)	0 (0.0)	0.117
Gastric ulcer	0 (0.0)	0 (0.0)	1 (10.0)	0.355
Paresis of recurrent laryngeal nerve	0 (0.0)	0 (0.0)	1 (10.0)	0.355
Diaphragm paralysis	0 (0.0)	1 (10.0)	0 (0.0)	0.355
Urosepsis	0 (0.0)	1 (10.0)	0 (0.0)	0.355
Takotsubo cardiomyopathy	1 (10.0)	0 (0.0)	0 (0.0)	0.355
Diarrhea	1 (10.0)	0 (0.0)	0 (0.0)	0.355
Breast abscess	1 (10.0)	0 (0.0)	0 (0.0)	0.355

Values are n (%)

markers underscores the need for continued exploration. The search for additional markers that capture the full spectrum of inflammatory processes is ongoing.

The present trial is a single center pilot study. More and more clinical studies investigating the effect of cell therapy are adding knowledge to the field. However, larger studies are warranted to explore the potential clinical effect of allogeneic ASC treatment in patients with an inflammatory component in their disease condition or in relation to organ transplantation as the lung.

Using ASCs compared to standard immunosuppressive treatment, may result in a local effect in donor lungs to reduce PGD without the side-effects related to standard immunosuppressive treatment. Moreover, ASC treatment may have the potential to reduce the amount of conventional given immunosuppressive treatment.

In conclusion, the present clinical study demonstrated some of the challenges by using ASCs as immune modulation in organ transplantation in a real-world setting.

Intravenous infusion of 200 million ASCs and 100 million ASCs compared to placebo infusion demonstrated to be safe. Post-hoc analysis showed a reduced progression in PGD grade from day 1 to day 3 and day 2 to day 3 in the ASC treated patients.

There were no significant differences in kidney function, inflammatory parameters, lung function or in quality-of-life scores.

Larger studies are needed to further explore the immune modulatory effect of ASC in lung transplantation along with safety.

Contributors

AM, MJ, AQ, TKL, PBJ, HM, CM, JK and MP were responsible for conceptualization and design of the study. AE, MJ, JK and MP applied for funding. AQ, TKL, PBJ, KJ, HM, CM, SR, AK, HB, JK and MP were involved in running the clinical trial. MHS, AE, MJ, EJ and LH were responsible for methodology, the cell therapy, product, randomization and blinding. TKL and MP PGD grading. AQ, TKL, TL, MJ, JK and MP verified the data and performed the statistical analysis beside contributing to the writing of the first draft.

All authors read and revised the manuscript for final approval. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Declaration of Competing Interest

Jens Kastrup, Annette Ekblond and Mandana Haack-Sørensen are inventors of a granted patent ("STEM CELL

THERAPY BASED ON ADIPOSE-DERIVED STEM CELLS" (WO2017068140A1 EP3365432A1) owned by the Capital Region of Denmark and Rigshospitalet, Copenhagen University Hospital, Denmark. The patent is granted in Europe and Australia. Applications are submitted in Canada, Hong Kong, Japan, Korea and USA.

Jens Kastrup, Annette Ekblond and Mandana Haack-Sørensen are the founder of Cell2Cure ApS, which has a license to commercialize the patent.

The authors declare no conflict of interest except above-mentioned.

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Data sharing

De-identified study data can be made available after a written request send to the corresponding author. The request will be evaluated after an approval by the Danish Data Protection Agency and shared via a secure data access system.

Appendix A. Supporting information

Supplemental data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2025.100254.

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