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Effect of mesenchymal stem cells on the host response in severe community-acquired pneumonia

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ABSTRACT

Mesenchymal stem cells (MSC) have immune regulatory properties that may ameliorate pathophysiological processes in sepsis. We determined the effect of allogeneic adipose-derived MSCs (Cx611) on the host response during sepsis due to community-acquired bacterial pneumonia (CABP) by measuring 29 plasma biomarkers and blood transcriptomes at six time points in 82 patients randomised to two intravenous infusions of Cx611 or placebo. Cx611 treatment enhanced several endothelial cell and procoagulant response plasma biomarkers, and led to increased expression of pathways related to innate immunity, haemostasis and apoptosis. Cx611 infusion in sepsis due to CABP is associated with broad host response alterations.

INTRODUCTION

In spite of decades-long efforts, therapeutics capable of ameliorating disease pathophysiology and improving patient-important clinical outcomes in sepsis and pneumonia remain elusive. Mesenchymal stem cells (MSCs)—multipotent cells that can contribute to tissue repair and modulate immune responses—exert a variety of effects on the pathophysiology of pneumonia and sepsis that have led to improved outcomes in preclinical models.[1] Several small phase I and II clinical trials have demonstrated the safety of treatment with MSCs in critically ill patients with sepsis and/or acute respiratory distress syndrome.[2 3] SEPCELL was a phase Ib/IIa clinical trial investigating the use of Cx611 (adipose-derived stem cells) in patients with severe community-acquired bacterial pneumonia (CABP), and the largest study on the effects of MSCs in this population conducted thus far.[4 5] We recently reported on the primary objective of SEPCELL—a favourable safety profile of Cx611 infusion in patients with severe CABP.[5] In the current preplanned ancillary study,[4] we aimed to assess the effect of Cx611 treatment on the host response by sequential measurements of plasma protein biomarkers—reflective of key pathophysiological processes—and blood transcriptomes.

METHODS

Adult patients (≥18 and ≤80 years old) were eligible for the study if there was a clinical suspicion of severe CABP, and if they needed mechanical ventilation (including high-flow oxygen) and/or vasopressor treatment. Patients were randomised to receive either two intravenous administrations of Cx611 (160×10^6 cells) or placebo (Ringer's lactate) at day 1 and day 3 of the study. We measured 29 protein biomarkers reflective of five pathophysiological domains (inflammation, inhibition of inflammation, apoptosis, endothelial cell responses and coagulation) before and at five time points after initiation of treatment (figure 1A, online supplemental table 1, online supplemental figure 1). We analysed the data using linear mixed models that adjusted for chance variation in baseline values between groups. Gene set enrichment analysis was done using the Reactome knowledgebase (reactome.org), focusing on predetermined pathways implicated in the pathogenesis of sepsis: immune system, apoptosis and haemostasis. Further details on study design, inclusion and exclusion criteria, sample collection and processing, and statistical analysis can be found in the online supplemental methods.

RESULTS

41 patients in both the Cx611 and placebo groups participated (online supplemental figure 2). Baseline characteristics and clinical outcomes were balanced between the groups (table 1, online supplemental table 2).[5] Figure 1B provides an overview of the effect of Cx611 infusion (relative to placebo) on all biomarkers measured in plasma obtained at five time points after treatment initiation (overview of all measurements in online supplemental table 3). The proportion of patients still in the study at the V9 time point was high and comparable between study groups (35/41 (85.4%)

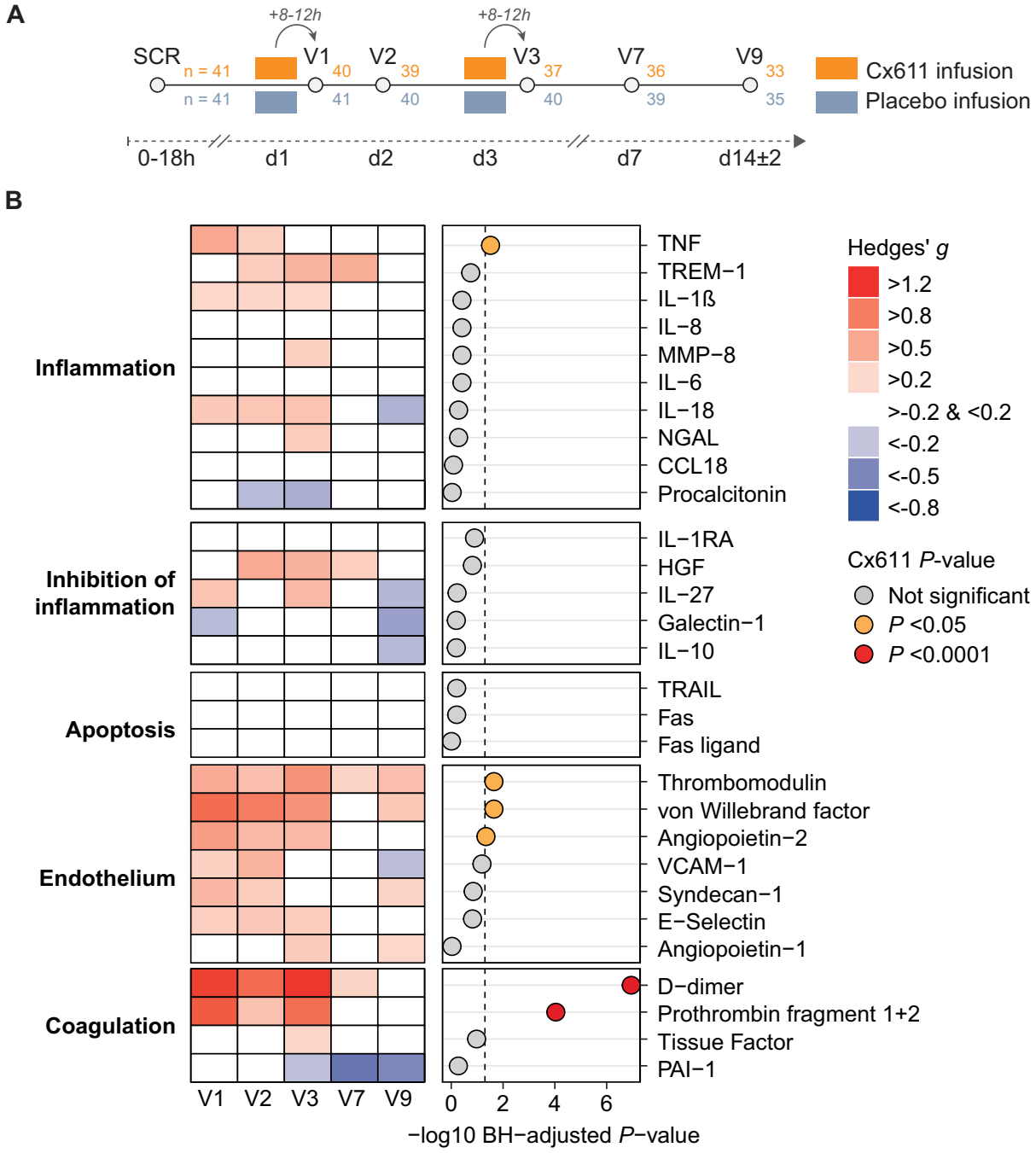

Figure 1 Overview of study design and effect of Cx611 treatment on plasma host response biomarkers stratified according to pathophysiological domains. (A) Overview of time points at which samples were collected for plasma protein and RNA biomarker analyses: within 18 hours of initiation of vasopressors and/or mechanical ventilation, prior to the initiation of treatment (screening/SCR), 8–12 hours following the initial infusion of Cx611 or placebo on day 1 (visit 1/V1), day 2 (V2), 8–12 hours following the second infusion of Cx611 or placebo on day 3 (V3), day 7 (V7) and day 14±2 (V9). Sample collection continued after intensive care unit (ICU) and hospital discharge. Number of samples available for plasma biomarker analyses listed to the right of each time point, Cx611-treated patients in orange, placebo-treated patients in blue/grey. (B) Heatmap showing the levels of each plasma protein host response biomarker, divided across five pathophysiological domains, for patients treated with Cx611 relative to patients treated with placebo at each time point after the initiation of treatment, expressed as an effect size (Hedges' *g*, red indicates higher values and blue indicates lower values in Cx611-treated patients). For visual purposes, comparisons with a Hedges' *g* >−0.2 and <0.2 (considered a negligible effect) are displayed as white tiles. To account for baseline variation in biomarker levels not attributable to treatment, we used the fold change from prior to treatment (screening/SCR time point) to each time point for each patient. The p values displayed to the right of heatmap are derived from a type II Wald test on linear mixed models for each individual biomarker (as described in the statistical analysis paragraph in the online supplemental methods), and indicate whether the overall effect of Cx611 on biomarker concentrations over all time points after initiation of treatment, adjusted for baseline variation in biomarker levels, is statistically significant. These p values were adjusted for multiple testing per domain using the Benjamini-Hochberg (BH) method. CCL, CC chemokine ligand; HGF, hepatocyte growth factor; IL-1RA, interleukin 1 receptor antagonist; MMP-8, matrix metalloproteinase 8; NGAL, neutrophil gelatinase-associated lipocalin; PAI-1, plasminogen activator inhibitor 1; TNF, tumour necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; TREM-1, triggering receptor expressed on myeloid cell 1; VCAM-1, vascular cell adhesion molecule 1.

Table 1 Baseline characteristics and outcomes

	Cx611 (n=41)	Placebo (n=41)
Demographics		
Age, years	60.9 (11.3)	63.4 (10.4)
Sex, male	27 (65.9%)	26 (63.4%)
Disease severity		
Randomisation stratum		
Invasive mechanical ventilation	22 (53.7%)	23 (56.1%)
Shock	14 (34.1%)	13 (31.7%)
Both	5 (12.2%)	5 (12.2%)
CURB-65	3 [2, 3]	3 [2, 4]
APACHE II score	20.2 (7.7)	18.9 (6.2)
SOFA score*	8 [7, 11]	8 [7, 9]
Outcomes†		
Any thromboembolic event‡	7 (17.1%)	8 (19.5%)
Length of intensive care unit stay	13 [6, 29]	11 [6, 19]
Length of hospital stay	20 [12, 44]	19 [14, 36]
28-day mortality	8 (19.5%)	6 (14.6%)

Normally distributed continuous variables are listed as mean (SD); non-normally distributed continuous variables are listed as median [IQR]; categorical variables are listed as count (%).
*All patients fulfilled the Sepsis-3 criteria (infection plus SOFA score of 2 or higher).
†A full overview of adverse events and clinical outcomes can be found in the primary clinical report.[5]
‡Individual patients could have more than one thromboembolic event. For the Cx611 group, this included deep vein thrombosis (n=3), pulmonary embolism (n=1), cerebrovascular accident (n=2), device-related thrombosis (n=1), atrial thrombosis (n=1) and cerebral artery embolism (n=1). For the placebo group, this included deep vein thrombosis (n=5), pulmonary embolism (n=2), venous thrombosis (n=1), venous thrombosis of a limb (n=1) and jugular vein thrombosis (n=1).
APACHE-II, Acute Physiology and Chronic Health Evaluation II; CURB-65, confusion, blood urea nitrogen, respiratory rate, blood pressure, age 65 or older; SOFA, Sequential Organ Failure Assessment.

for Cx611, 38/41 (92.7%); online supplemental table 1). Despite the anti-inflammatory and antiapoptotic effects of MSCs reported in preclinical studies,[1] we found few differences in biomarkers reflective of inflammation, inhibition of inflammation or apoptosis (online supplemental figures 3–5). Only tumour necrosis factor—a quintessential proinflammatory cytokine—was significantly higher in patients treated with Cx611 (p=0.030), driven by the time frame spanning stem cell infusion (V1–V3). With regard to endothelial cell biomarkers, the plasma concentrations of von Willebrand factor (reflecting endothelial cell activation), soluble thrombomodulin (endothelial cell injury) and angiopoietin-2 (disturbed barrier function) were higher in patients infused with Cx611 at time points up to V3 (ie, 8–12 hours after the second drug infusion; online supplemental figure 6). Moreover, Cx611 induced a procoagulant state in this time frame, as indicated by strong increases in the plasma levels of prothrombin fragment 1+2 (thrombin formation) and D-dimer (fibrin formation and fibrinolysis).

Analysis of blood transcriptome data revealed that Cx611 induced a predominantly proinflammatory state, detectable from day 2 after the initiation of treatment (V2) up to 4 days after the second treatment (V7; figure 2, online supplemental figure 7, online supplemental table 4). In the innate immune system pathways, we found upregulation of pattern recognition receptor pathways such as toll-like receptors, accompanied by upregulation of pathways related to innate immune effector functions, such as neutrophil degranulation (online supplemental figure 8). Innate immune activation was further corroborated by upregulation of pathways related to key growth factors involved in emergency myelopoiesis (granulocyte and granulocyte-macrophage colony-stimulating factors, and interleukin 3) and proinflammatory cytokine signalling (figure 2). In the adaptive immune system, Cx611-treated patients exhibited upregulation of pathways related to major histocompatibility complex class I antigen presentation, suggesting activation of cellular immunity, specifically cytotoxic CD8 T cells (figure 2, online supplemental figure 8), while downregulation of pathways related to T cell receptor signalling and reduced CD28 costimulation pointed at impaired T cell activation. However, downregulation of signalling through the inhibitory immune checkpoint programmed death 1 in Cx611-treated patients argued against adaptive immunosuppression. A more detailed overview of the plasma biomarker and transcriptomic results—including the modest upregulation of pathways related to apoptosis, endothelial cell surface interactions and haemostasis—can be found in online supplemental figures 9 and 10.

DISCUSSION

We report the largest and most comprehensive study on the effect of MSCs on the immune response in critically ill patients, but there are limitations to consider. The study was exploratory in nature and the total intended sample size was not calculated specifically to detect differences in biomarker levels. While the risk of attrition bias is low, informative censoring due to death or withdrawal from the study may have resulted in some residual bias not fully addressed by linear mixed models. A replication cohort in this patient population did not exist at time of analysis, and the results could therefore not be validated externally.

While there were no adverse events related to Cx611 infusion,[5] Cx611 treatment resulted in transient proinflammatory effects mainly relating to enhanced activation of the endothelium and coagulation system, and increased expression of gene pathways involved in pattern recognition receptor and cytokine signalling, haemostasis and apoptosis. Our results may in part be indicative of recognition of intravenously introduced MSCs by the host immune system. The proinflammatory effects reported here contrast with the anti-inflammatory effects reported in the preponderance of preclinical studies.[1] However, previous clinical studies that reported biological outcomes were small and have not conclusively demonstrated anti-inflammatory effects of MSCs in critically ill humans.[6–8] The adipose origin of Cx611 may play a part, but clear evidence that the immune regulatory properties of adipose-derived MSCs are different from those of MSCs of other origins is not available. Although a higher expression of tissue factor on adipose-derived MSCs[9] could indicate a higher procoagulant potential, procoagulant responses have also been reported for MSCs of other origins.[10] It remains to be established which effects of MSCs on the host response in patients with sepsis due to CABP would be beneficial for clinical outcomes, and which could potentially do harm.

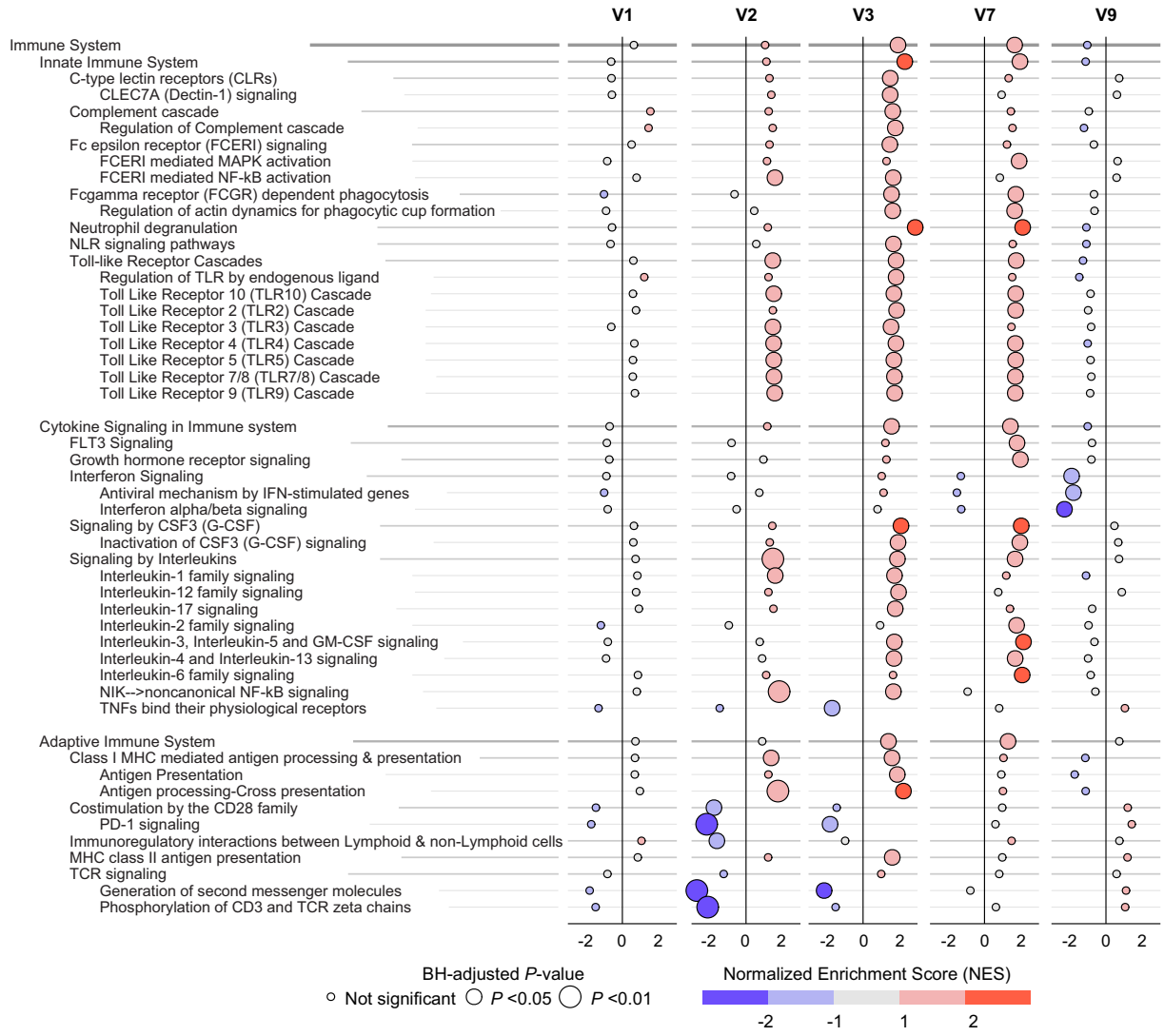

Figure 2 Significant immune system pathways from gene set enrichment analysis of the blood transcriptome. Bubble plot displaying the effect of Cx611 treatment on transcriptional pathways related to the immune system (as obtained from the Reactome knowledgebase) for each time point after the initiation of treatment with Cx611 or placebo. To adjust for chance variation in baseline gene expression between groups, the differences in gene expression at each time point are derived from the interaction terms between Cx611 and time point in linear mixed models that included the SCR time point (prior to initiation as treatment) as the reference category, and can therefore be interpreted as the difference in gene expression levels between groups at each time point relative to the gene expression levels prior to initiation of treatment. The differences in expression of genes in the listed pathways are quantified as NES and reflected in the intensity of the colour: a red bubble means higher in the Cx611-treated group, a blue bubble means lower in the Cx611-treated group and a grey bubble indicates a negligible difference. The size of the bubble is proportional to the Benjamini-Hochberg (BH)-adjusted p value for that pathway. This figure only includes pathways in which a significant difference between groups was found at one or more time points; the full version of the figure including non-significant pathways can be found in online supplemental figure 7. CLEC7A, C-type lectin domain family 7 member A; Fc, fragment crystallisable region (of an antibody); FLT3, fms-related receptor tyrosine kinase 3; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NIK, NF-κB-inducing kinase; NLR, nucleotide-binding domain leucine-rich repeat containing receptor; PD-1, programmed death 1; TCR, T cell receptor; TNF, tumour necrosis factor.

Correction notice This article has been corrected since it was published Online First. A collaborator name has been corrected.

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Contributors P-FL, BF, MSG, EL and TvdP designed and delivered the SEPCELL clinical trial. TDYR, JMB, BPS and TvdP conceived and designed the host response ancillary analyses. P-FL, BF, MSG, TDYR, TSRvE, KJG, DVO and DS contributed to the acquisition and quality control of the clinical and/or biological data. TDYR, JMB and KJG performed the analyses. TDYR and TvdP drafted the manuscript. All authors critically revised and approved the manuscript.

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Competing interests DVO, KJG and EL are employed by Takeda Pharmaceuticals, which produces Cx611.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the independent ethics committees of the participating hospitals: Comite de Protection des Personnes Sud-Ouest et Outre-Mer II, Agence Régionale de Santé Occitanie (Dossier 2-18-08); Comité d'Éthique Hospitalo Facultaire, Cliniques Universitaires Saint-Luc, Université catholique de Louvain (2015/13NOV/618); Comité Etica Regional de la Comunidad de Madrid (Cx611-0204/2015-002994-39). Written informed consent was obtained from all patients, their legal representative or next of kin. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement RNAseq data are available from the NCBI Sequence Read Archive (SRA) under the BioProject accession PRJNA1097551. Other data generated and/or analysed during the current study are available on reasonable request.

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