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First-in-man use of a cardiovascular cell-derived secretome in heart failure. Case report



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Summary

Background There is increased evidence that the effects of stem cells can mostly be duplicated by administration of their secretome which might streamline the translation towards the clinics.

Methods The 12-patient SECRET-HF phase 1 trial has thus been designed to determine the feasibility and safety of repeated intravenous injections of the extracellular vesicle (EV)-enriched secretome of cardiovascular progenitor cells differentiated from pluripotent stem cells in severely symptomatic patients with drug-refractory left ventricular (LV) dysfunction secondary to non-ischemic dilated cardiomyopathy. Here we report the case of the first treated patient (baseline NYHA class III; LV Ejection Fraction:25%) in whom a dose of 20×10^9 particles/kg was intravenously infused three times three weeks apart.

Findings In addition to demonstrating the feasibility of producing a cardiac cell secretome compliant with Good Manufacturing Practice standards, this case documents the excellent tolerance of its repeated delivery, without any adverse events during or after infusions. Six months after the procedure, the patient is in NYHA Class II with improved echo parameters, a reduced daily need for diuretics (from 240 mg to 160 mg), no firing from the previously implanted automatic internal defibrillator and no alloimmunization against the drug product, thereby supporting its lack of immunogenicity.

Interpretation The rationale underlying the intravenous route is that the infused EV-enriched secretome may act by rewiring endogenous immune cells, both circulating and in peripheral organs, to take on a reparative phenotype. These EV-modified immune cells could then traffic to the heart to effect tissue repair, including mitigation of inflammation which is a hallmark of cardiac failure.

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Keywords: Heart failure; Dilated cardiomyopathy; Extracellular vesicles; Secretome; Cardiovascular progenitor cells; Case report

Research in context

Evidence before this study

Most of the effects of stem cells can be duplicated by administration of the bioactive molecules that they release (the secretome). While the benefits of this secretome on cardiac structure and function have been extensively demonstrated in preclinical models of cardiomyopathies, concerns have been raised about the technical challenges of turning this secretome into a clinically useable product.

Added value of this study

This study is the first to demonstrate, in the context of cardiac diseases, the feasibility of leveraging the paracrine effects of cardiovascular progenitor cells differentiated from induced pluripotent stem cells to a Good Manufacturing Practice-compliant therapeutic product. The study also provides an encouraging safety signal in that the first patient in whom the secretome was repeatedly administered did not

show any adverse event and, more specifically, had no evidence for an acute infusion-related immune-inflammatory response or delayed alloimmunization.

Implications of all the available evidence

A full assessment of the safety and efficacy of these secretome infusions will only be possible at the end of the ongoing open-label phase 1 dose-escalating trial (SECRET-HF) but the study yet paves the way for a possible novel user-friendly treatment of severe heart failure. The intravenous route features several clinically relevant advantages (lack of invasiveness, possibility of repeated treatments, low cost) and the rationale underlying this approach is a potential secretome-induced systemic modulation of the immune system with subsequent remote benefits in the heart given the role of immune dysregulation as a driver of heart failure.

Introduction

When cardiac cell therapy first began, the premise was that the transplanted cells would integrate into the recipient myocardium and build a force-generating contractile tissue. It is now recognized that this “regeneration” is unlikely to occur because, regardless of the pre-transplantation processing of the cells, they fail to survive long term.¹ However, the observation that the functional benefits of stem cells, intramyocardially transplanted, commonly outlast their limited engraftment time² has led to the hypothesis that their primary mechanism of action is the release of a blend of biomolecules, many of which are packed into extracellular vesicles (EV), which induce endogenous repair pathways through a paracrine mechanism.¹ In line with this hypothesis, we have shown that the transplantation of embryonic stem cell-derived cardiovascular progenitor cells, similar to those successfully tested in our ESCORT trial (NCT02057900),³ or the exclusive intramyocardial injection of their secretome yielded equivalent outcomes with regard to left ventricular (LV) function and activation of intramyocardial cardio-reparative signalling pathways.⁴ We then moved towards a series of experiments to better characterize this acellular secretome,^{5–8} at the completion of which we developed an at-scale, current Good Manufacturing Practices (CGMP)-compliant manufacturing process for stem cell-derived cardiac progenitor cells (CPC), and produced an Investigational Medicinal Product (IMP) which comprises the EV-enriched secretome of these CPC. Such a product has not yet been tested in heart failure. The first-in-man Phase I, open-label, single-centre SECRET-HF trial

(NCT05774509) has thus been designed to assess the effects of three intravenous infusions of this IMP, three weeks apart, in severely symptomatic patients with drug-refractory LV dysfunction secondary to non-ischemic dilated cardiomyopathy. This report describes the case of the first included patient.

Methods

The IMP tested in SECRET-HF comprises the EV-enriched secretome from CPC differentiated from human induced pluripotent stem cells (iPSC). These iPSC were reprogrammed from the somatic cells of a single, healthy donor, expanded, and banked using CGMP proprietary processes developed and owned by FUJIFILM Cellular Dynamics, Inc. (FCDI). Vials of iPSC from a single CGMP working cell bank were cultured and differentiated to CPC using proprietary CGMP processes developed by FUJIFILM Cellular Dynamics, Inc. (FCDI), at the FCDI Innovation Facility for Advanced Cell Therapy (Madison, WI, USA). We have previously shown by both qPCR and immunostaining that research-grade iPSC-derived CPC from FCDI show a reduced expression of the pluripotency markers NANOG, SOX2, OCT3/4, the expression of the early cardiovascular lineage markers ISL-1, MEF2C, NKX2.5 and GATA4, and the absence of mature cardiomyocyte markers such as TBX20, TNNT2, PLN, MYH6, MYH7, MYL2.⁶ Two separate banks of cryopreserved CPC were generated from vials coming from the same iPSC bank lot. The CPC underwent extensive quality control testing (ex. viability, identity, purity, sterility, genomic integrity,

adventitious agent screening) after which the cryopreserved cells were shipped to the MEARY Cell and Gene Therapy Center (*Assistance Publique-Hôpitaux de Paris*, Paris, France), where they were thawed and further quality-tested for viability (by an automated cell counter), identity (by flow cytometry) and sterility (by microbiological testing, all according to the European Pharmacopea). The thawed CPC were then cultured in multi-layer culture flasks (CellSTACK®, Corning, Glendale, AZ), in a “vesiculation” medium designed to minimize any contribution of the culture media component in the final product. The conditioned media were collected and underwent in-process testing including the number and size of particles (by Nano-particle Tracking Analysis [NTA] using the NanoSight, LM10, Malvern Panalytical, Malvern, UK); EV marker identity (CD9, CD63 and CD81, assessed by flow cytometry using the MACSPlex Exosome kit #130-108-813; Miltenyi Biotec, Bergisch Gladbach, Germany); protein concentration (by the bicinchoninic acid assay) and sterility (by aerobic and anaerobic assays). The EV-containing conditioned medium was filtered, enriched for EV, and concentrated by tangential flow filtration (TFF, Allegro™ CM150; PALL/Sartorius, Göttingen, Germany) using a molecular weight cut-off (MWCO) of 30 kDa, which retained the small EV fraction and large secreted proteins. The retentate was filter-sterilized (0.22 µm) and aliquoted into 2-mL glass vials which were stored at -80 °C. Samples of the final clinical-grade drug product were quality-tested for the number and size of particles (by NanoSight); EV marker identity (CD9, CD63 and CD81; MACSPlex Exosome kit; same reference as above); sterility (by aerobic and anaerobic assays); endotoxin and mycoplasma detection (by a

chromo LAL kit and a quantitative Polymerase Chain Reaction assay, respectively); *in vitro* potency (by a cell proliferation assay); *in vitro* immunogenicity; visual inspection/appearance; and stability (by checking the maintenance of particle number and potency). These *in vitro* controls were completed by Good Laboratory Practice (GLP) animal studies designed to assess toxicity and oncogenicity *in vivo*; despite a 10-fold higher dose than the anticipated maximum human dose, none of the mice and rats injected with the CPC-derived EV-enriched secretome exhibited changes in hematology and clinical chemistry parameters, changes in organ weight or macro/microscopic findings suggestive of toxicity; likewise, the administration of the secretome in immune-deficient mice induced no tumors during the 91-day observation period and did not produce proliferative changes either. Efficacy non GLP animal studies conducted in our laboratory were approved by the Institutional Ethics Committee of the University (#15616 and #33136) and complied with European legislation (European Commission Directive 2010/63/EU) on animal care.

At the time of use, the IMP was thawed and prepared for use in the hospital pharmacy (*Pharmacie à Usage Intérieur*) under controlled conditions. After the perfusion bag had been filled with the weight-adjusted dose, aliquots of the remaining EV-enriched secretome were harvested from the 2-mL vials and processed by NTA which displayed spectra both typical for EV and well reproducible from one perfusion to the next one (Fig. 1).

The primary outcome measure of the trial is the number of any potentially serious adverse events (SAEs) or reactions recorded after each infusion and up to one year thereafter. A maximum of 12 patients are planned

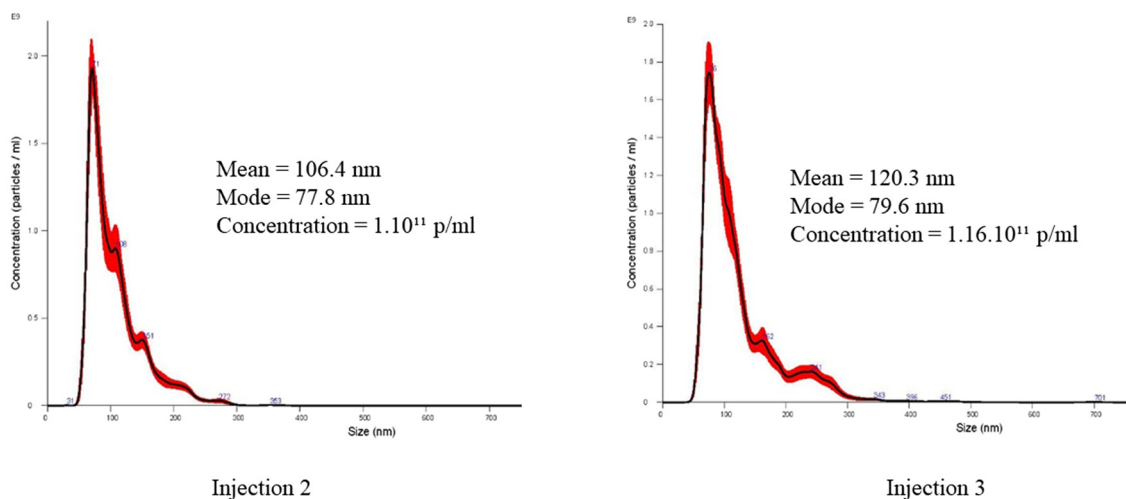


Fig. 1: Representative NTA spectra of aliquots of the EV-enriched secretome given to the patient. Samples of the secretome were taken at the time of the second and third infusions from the media remaining in the thawed vials after the patient-specific dose adjustment had been completed and show both the typical display of EV and a good vial-to-vial reproducibility.

with dose escalation using the Bayesian optimal interval (BOIN) design exploring, according to the occurrence or not of dose-limiting toxicity (DLT), two dose levels: the first one consisting of three infusions of 20×10^9 particles/kg each and the second one, of three infusions of 40×10^9 particles/kg each, which represents the equivalent of the secretome recovered from 1 to 2 million cells/kg of recipient body weight per infusion, respectively. Safety data are monitored by a dedicated Committee comprising Dr Clara Locher (Rennes), Prs Michel Desnos (Le Plessis-Robinson, France), Stefan Janssens (Louvain, Belgium) and Alexandre Mebazaa (Paris, France).

The first patient was a 59-year old male who was followed for a non-ischemic dilated cardiomyopathy due to a pathogenic mutation of the tropomyosin gene. At the time of referral, he was in New York Heart Association (NYHA) class III, despite an optimal guideline-directed medical therapy. He had been previously implanted with a prophylactic automatic internal cardioverter defibrillator (AICD). As he declined to be listed for transplantation, he was offered to be included in the SECRET-HF trial, and he gave his informed consent. At the time of inclusion, the physical examination was unremarkable. He was in sinus rhythm and tri-dimensional echocardiography showed LV end-diastolic (LVEDV) and end-systolic (LVESV) indexed volumes of 110 mL/m^2 and 82 mL/m^2 , respectively, with an ejection fraction (EF) of 25%. The peak VO_2 was 13.4 mL/kg/min (47% of the theoretical value) and this end point was preferred to the 6-min walk test because of its higher predictive value of adverse cardiac events.⁹ The coronary arteries were disease-free on the angiogram. The day of treatment, the required number of the secretome-containing vials were thawed and injected into a 50-mL bag of sodium chloride. The three secretome infusions (20×10^9 particles/kg each) were performed three weeks apart through an intravenous peripheral line in the Intensive Care Unit (*Hôpital Européen Georges Pompidou*, Paris, France), under continuous monitoring of heart rate, blood pressure and oxygen saturation. Each infusion was preceded by an intravenous premedication by a bolus of anti-histaminic drug and methylprednisolone.

The Ethics Review Board of Île-de-France V approved the trial (22.03185.000111). The proprietary methods of the iPSC differentiation and EV production as well as the protocol were reviewed by the French Regulatory Agency (*Agence nationale de sécurité du médicament et des produits de santé*, ANSM) which approved the study on February 2, 2023 (EUDRACT: 2022-001844-75; ClinicalTrials.gov ID NCT05774509).

Funding

This trial is funded by the French Ministry of Health (*Programme Hospitalier de Recherche Clinique AOM19330*) and the “France 2030” National Strategy

Program (ANR-20-F2II-0003). It is sponsored by *Assistance Publique-Hôpitaux de Paris*. Neither the funder nor the sponsor were involved in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

Overall, the procedure was found to be safe on the basis of an array of observations: (1) All infusions were well tolerated without SAEs, allowing for rapid discharge; (2) there has been no post-treatments ventricular arrhythmias detected by the AICD; (3) neither the numeration of lymphocyte subpopulations by flow cytometry nor the cytokine assays by luminex technology at the different time points showed evidence for secretome-induced inflammation; (4) the C-Reactive Protein decreased from 15.6 mg/L from before the first infusion to 1.9 mg/L after the third one; (5) since HLA typing of the original iPSC donor was available, donor-specific antibody (DSA) testing was repeated 2 weeks after each infusion (hence the 3-week interval between treatments to give time for a potential increase in antibodies and avoid reinfusion in case of DSA detection with a Mean Fluorescence Intensity >5000) and 28 days post-treatment. None of these assays showed an alloimmunization against the drug product.

Six months after the last infusion, the patient is in NYHA Class II with a reduced daily dosing of diuretics (from 240 mg to 160 mg) and a substantial improvement in the Minnesota Living With Heart Failure (MLHF) Questionnaire the score of which has decreased from 45 (baseline) to 28. Echo parameters values have improved from baseline with a decrease in LVEDV and LVESV (from 110 mL/m^2 to 88 mL/m^2 and from 82 mL/m^2 to 60 mL/m^2 , respectively) and a concomitant increase in LVEF from 25% to 32%. NT pro-BNP values have decreased from 2261 ng/L (before the first infusion) to 1136 ng/L . The ^{18}F -fluoro-2-deoxyglucose (^{18}F FDG) positron emission tomography (PET), planned per protocol, has not shown any abnormality compared with the pre-treatment one.

Discussion

The SECRET-HF trial has been developed on the basis of three major observations in animal models: (1) the cellular secretome, which contains soluble factors and EV, can duplicate the effects of their parental cells, an observation now made across a wide variety of preclinical disease models¹⁰; (2) the best outcomes seem to come from EV derived from immature cells phenotypically close to those of the tissue to repair,¹¹ hence our choice of CPC as the EV donors; (3) this secretome still retains its cardio-reparative properties when given intravenously,⁵ thereby enabling convenient repeated administrations.

This case report illustrates the translatability of these concepts into a clinically useable drug product by showing the feasibility of its manufacturing under CGMP conditions at a Phase I clinical scale and documents, for the first time in the context of heart failure, the short-term safety of repeated intravenous delivery of the IMP and, more specifically, the lack of immune-inflammatory response or alloimmunization subsequent to repeated doses. This supports the idea that, in contrast to allogeneic pluripotent stem cell therapy, secreted EV are not immunogenic.⁷ The stability of this secretome product after cryo-storage enables its off-the-shelf use, which is a significant advantage over a cellular product, as discussed elsewhere.¹⁰ Furthermore, while mesenchymal stromal cell-derived EV-enriched secretomes have been shown to be effective in preclinical studies,¹² our choice of using EV-producing cells derived from an iPSC line was aimed to better address the challenge of batch to batch reproducibility, as discussed below.

The mechanisms by which intravenously delivered EV could be a disease-modifying cardio-protective intervention still remain unsettled in view of their preferential biodistribution in the liver, spleen and lungs. However, the consistent observation that an intravenous delivery route can be functionally effective in heart,⁵ brain and kidney models¹⁰ has led to the speculation that infused EV act by rewiring endogenous immune cells, both circulating and in peripheral organs, to take on a reparative phenotype.¹³ These EV-modified immune cells could then travel to the heart to carry out the reparative processes they were instructed to do by the therapeutic vesicles, including the mitigation of inflammation¹⁴ which is a hallmark of cardiac failure.¹⁵

While no efficacy conclusions can be drawn from a single case, this report yet documents that the CGMP manufacturing of a cellular secretome can be successfully achieved. Nevertheless, several key issues still require further consideration. Three of them deserve to be specifically discussed. The first pertains to the challenge of generating reproducible batches of the cell-derived secretome. In contrast to conventional chemically-derived drugs, biopharmaceuticals rely on biological processes, where even small changes to the production process can have potentially unpredictable and possibly profound effects on the final critical product attributes (hence the formula: “the product is the process”). In the SECRET-HF trial, a first measure to address this issue has been to derive the CPC, used as the source of the secretome, from a cell line (iPSC) rather than from primary cells. The secretome was then produced through a sequence of carefully standardized steps with several in-process quality controls. Finally, to ensure that all patients would receive an identical IMP composition with an excellent safety profile, a single lot of product was

generated to serve the GLP toxicity and oncogenicity animal studies and the entire 12-patient trial.

A second issue pertains to dosing. There is currently no consensus regarding the optimal metrics for EV dosing: number of particles quantified by NTA (which can be misleading because the equipment counts all particles, some of which are not EV), weight of the exosome suspension, amount of infused volume or cell equivalents. In the SECRET-HF trial, we used the latter, starting from the observation that the functional equivalence between cells and their secretome could justify using an amount of secretome equivalent to the one which would be theoretically released by a therapeutic dose of cells. In the clinic, the cells that have been mostly delivered intravenously are mesenchymal stromal cells at doses usually ranging from 1 to 2 million cells/kg of body weight.¹⁶ We have thus chosen to conservatively start with a secretome dose equivalent to the theoretical production of 1 million CPC/kg of body weight (cohort 1) and, in the absence of safety issues in this cohort, have planned to increase dosing to the equivalent of the secretome from 2 million CPC/kg of body weight (cohort 2). Having quantified the average number of particles released per CPC ($\approx 20,000$ particles/cell), simple mathematical calculations have determined the doses of 20×10^9 particles/kg and 40×10^9 particles/kg for each of the two patient cohorts, respectively. There are currently several EV clinical trials spanning a wide range of diseases and which differ by cell source, route of delivery, and dosing. Hopefully, their outcomes will allow to fine-tune the optimal dose range associated with the most profound disease-modifying effects in the future, keeping in mind that high doses may not necessarily be the most therapeutically effective because they may trigger an upregulation of EV lysosomal degradation.¹⁷

The third issue is related to the optimal degree of purification of the cell-conditioned medium. Although EV are largely accountable for the protective effects of their parental cells, other components (soluble factors, proteins) of the secretome might also contribute to the structural and functional preservation of the diseased hearts through their interactions with the cardiomyocytes and/or the extracellular matrix.^{18,19} In this study, we used TFF which is currently the only clinically-useable efficient method for producing EV-enriched formulations from large sample volumes.²⁰ As our own early development work found that a more restrictive EV isolation protocol (with higher MWCO) reduced the effects of the secretome, *in vitro*, the lower MWCO of 30 kDa was selected so as to retain the small EV and a portion of the larger secreted proteins. Other studies further support this idea that the deconstruction of the secretome product could be counterproductive; in a rat model of myocardial

infarction, although both the exosomal and protein fractions of the conditioned medium equally improved cardiac function, the best outcomes were found when the combination of fractions was used.²¹ However, if, in the future, a limited number of components could be identified as the key drivers of the therapeutic effects, one could envision a more stringent fractionation of the secretome, or defined combination of multiple active components into a synthetic drug.

As the SECRET-HF clinical trial continues to enrol patients, it will hopefully confirm the encouraging safety result yielded by this first case and help assess whether this acellular approach, more easily manageable in the clinic than whole cells, is therapeutically efficacious in patients with heart failure.

Contributors

PM and AH designed and conducted the trial, and wrote the case report; NR oversaw early process and analytical development for CPC differentiation and EV manufacture, oversaw CGMP manufacture of the CPC, and supported regulatory submissions for the clinical trial; AH and TP managed the patient before and after treatment; AB oversaw the logistics of the trial; PM and VB supervised the preclinical steps of the program; CH and GC led late-stage development of the CGMP EV manufacture process and QC release assays; CH, GC and JL participated in the IMP manufacture and supported regulatory submissions for the clinical trial; LL and BS ensured the final preparation of the IMP; HB performed and interpreted the in-process onco-molecular studies; CG and NB performed and interpreted the flow cytometry and luminex-based cytokine assays. All authors read and approved the final version of the manuscript.

Data sharing statement

De-identified data will be made available with publication upon request to the corresponding author. Additional requests related to the production process should be forwarded to either Nisa Renault (nisa.renault@fujifilm.com) or to the corresponding author.

Declaration of interests

PM is a consultant for Help Therapeutics and FCDI. NKR is a full-time employee of FCDI. No other author reports a conflict of interest. Two patents ("Generation of secretome-containing compositions", and "Methods of using and analyzing the same"; PCT/IB2021/00793 and PCT/US2023/035616) co-owned by FUJIFILM Corporation and Assistance Publique-Hôpitaux de Paris are currently pending.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ebiom.2024.105145>.

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