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ESC Heart Failure (2024)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.15124

STUDY DESIGN

Transendocardial injection of expanded autologous CD34+ cells after myocardial infarction: Design of the EXCELLENT trial

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Abstract

Aims The extent of irreversible cardiomyocyte necrosis after acute myocardial infarction (AMI) is a major determinant of residual left ventricular (LV) function and clinical outcome. Cell therapy based on CD34+ cells has emerged as an option to help repair the myocardium and to improve outcomes. The dose of CD34+ cells and the route of administration are two important factors that will determine the clinical effectiveness of the approach, provided it is robust and feasible. Here, we describe the rationale and design of the multicentre open-label randomized controlled phase I/IIb trial evaluating the safety and the likelihood of efficacy of transendocardial expanded CD34+ cell administration in patients presenting with AMI and a reduced LV ejection fraction.

Methods Patients with a large AMI and LV ejection fraction <50% are randomized 3:1 to transendocardial expanded CD34+ cell injection plus standard of care or standard of care alone. Patients randomized to intervention are treated with lenograstim for 5 days before 220 ± 10 mL blood cell harvest from which autologous CD34+ cells are purified and expanded for 9 days using an automated good manufacturing practice compliant platform. The primary endpoint is the incidence of major adverse cardiac events over 6 months. The main secondary endpoints are LV end systolic volume index and the viability of the infarcted segments.

Conclusions Autologous CD34+ cell therapy is currently limited by technological constraints. This is the first trial to evaluate the feasibility and potential effect of CD34+ cells after automated expansion and transendocardial administration in patients with large AMI.

Keywords Myocardial infarction; Repair and regenerative therapy; Autologous CD34+ cells; Cell expansion; Transendocardial injection

Received: 17 July 2024; Revised: 26 September 2024; Accepted: 1 October 2024
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Introduction

Acute myocardial infarction (AMI) is a leading cause of heart failure associated with an increased risk of morbidity and mortality.[1,2] Since the era of primary percutaneous coronary intervention (PCI) and optimal standard of care,[3,4] the rates of cardiovascular death and hospitalization for heart failure dropped to about 3%–4% per year[5,6] but are expected to reach 15% per year in patients cumulating multiple risk factors.[7]

Cell-based therapies have emerged in the early 2000s as a promising option to repair and regenerate heart tissue.[8] Several clinical studies reported that therapeutic administration of progenitor cells after AMI may improve ventricular remodelling, inflammation, apoptosis, cardiomyocyte regeneration, viability and left ventricular (LV) function.[9–11] However, the improvement of heart function is lower than expected due to several factors that may impact the therapy's benefits. These include enrolment criteria and endpoint heterogenicity,[12] patient-related factors such as active smoking, the absence of microvascular obstruction (MVO),[10] or the dose and type of cells.[13]

CD34+ cells can promote the formation of vascular structures and have a paracrine role in the stimulation of angiogenesis and vasculogenesis, the remodelling of extracellular matrix and the activation of additional progenitor cells.[14,15] A pilot study in seven patients with AMI showed that local delivery of peripheral blood derived CD34+ cells to the injured myocardium was feasible. In these patients, improvements of heart function parameters were apparent at 3 months post-transplant, with LV ejection fraction (LVEF) values progressively increasing with time.[16] Trials conducted in patients with ST segment elevation myocardial infarction (STEMI) and LV dysfunction confirmed that infusion of autologous CD34+ cells was safe and had a positive effect on the change in LVEF and infarct size. This positive effect was dose dependent, suggesting that a sufficient number of cells needs to be administered.[17,18] However, CD34+ cells have limited growth potential and a tendency to differentiate in culture; thus, making their ex vivo expansion a challenge.[19] The development of a highly efficient protocol for ex vivo expansion is required to achieve sufficient numbers of CD34+ cells.

The route of administration of the cells also plays an important role in the level of retention of cells in the damaged tissue. Transendocardial injection delivers the cells directly into the heart muscle, overcoming the limitations of intracoronary injection.[20]

The StemXpand® industrialized platform has been developed for the reproducible large-scale expansion of autologous CD34+ cells under good manufacturing practice (GMP). A study in healthy volunteers showed that the expansion process led to an average 19.1 ± 7.5-fold increase in the number of CD34+ cells. The expanded CD34+ cell identity, genetic stability and telomere length were consistent with those of non-expanded CD34+ cells.[21] These reports paved the way to clinical studies assessing the efficacy of the transendocardial injection of industrialized expanded autologous CD34+ cells, called ProtheraCytes®, in post-AMI patients.

The aim of the EXpanded CELL ENdocardiac Transplantation (EXCELLENT) open-label randomized, controlled phase I/IIb trial (NCT02669810) is to evaluate the safety and first efficacy trends of autologous expanded CD34+ cells administered through transendocardial injections to patients with large AMI and reduced LVEF.

Trial design

This is a multicentre phase I/IIb randomized, open label, controlled trial performed at 13 clinical sites in France and the United Kingdom. Patients are randomized 3:1 to receive transendocardial injections of expanded autologous CD34+ cells plus standard of care or the standard of care alone (*Figure 1*). Standard of care is expected to be compliant with current guideline-directed medical therapy for patients following AMI associated with LV dysfunction.

Trial population

Eligibility criteria are (i) AMI with or without ST segment elevation, (ii) elevation of plasma cardiac troponin concentration ≥70 times the upper reference limit, (iii) LVEF <50% and (iv) akinetic or dyskinetic LV segments at cardiac echography 2 days after AMI. Patients must be ≥18 and ≤85 years old, non-pregnant and on efficacious contraception in women of child-bearing potential. Inclusion criteria are a persistent LVEF <50%, and the identification of non-viable (transmural scar extend >50%), akinetic (no cardiac wall thickening during systole) or dyskinetic (cardiac wall thickening in the wrong orientation during systole) LV segments assessed by cardiac magnetic resonance (CMR) 8 (±3) days after AMI. Full inclusion and exclusion criteria are listed in *Table 1*.

The EXCELLENT trial complies with the Declaration of Helsinki and was approved by local research ethics committees. Patients must provide written informed consent, and eligible participants are randomized as soon as possible.

Objectives

The primary objective is to assess the incidence of adjudicated major adverse cardiac events (MACE) from randomization to 6 months. The main secondary objective is to establish the efficacy of the treatment intervention from randomization to 6 months. The other secondary objective is to determine the benefit/risk profile of the interventional procedure from randomization to 6 months. The components of the primary and secondary endpoints are described below.

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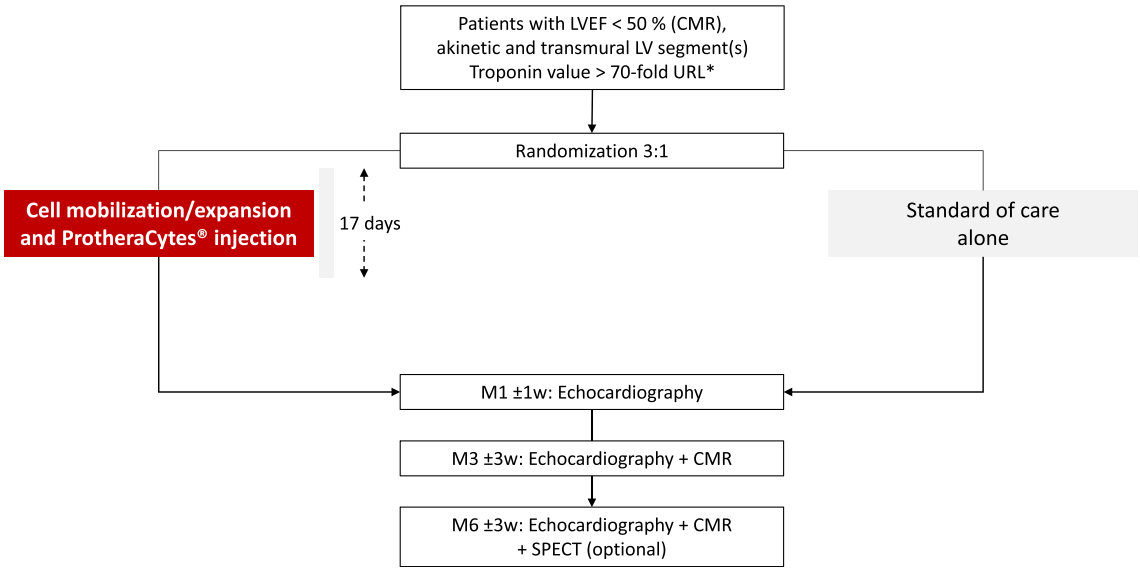
Figure 1 Design of the EXCELLENT trial. *Upper reference limit. CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction; M, month; SPECT, single photon emission computed tomography; w, week.



Manufacturing

Expanded CD34+ cells (ProtheraCytes®; CellProthera, France) are manufactured as described previously[21] in licensed cell therapy centres (CTC) in France and the United Kingdom (*Figure 2*). Following randomization and within 45 days after MI, patients are initially treated with lenograstim, a G-CSF agonist, for 5 days before a whole blood harvest of 220 ± 10 mL is withdrawn by venopuncture. If white blood cell counts at the fourth or fifth day exceed 60 × 10^9/L, lenograstim administration is withheld. In such situations, leucocytosis monitoring and hepatic enzyme analysis must be performed to verify a return to normal values. Whole blood harvest is performed at the ward authorized for blood harvesting and constitutes the starting material of the manufacturing process. It is immediately sent to the CTC for the first phase of the manufacturing process, CD34+ cell purification via immunoselection. Immunoselected CD34+ cells are then expanded in the StemXpand® device as previously described.[21] Briefly, purified CD34+ cells are seeded into a dedicated culture bag containing StemFeed (CellProthera, France) inside the StemXpand® device and cultured for 9 days at 37°C 5% CO_2. After expansion, a second immunoselection is conducted, and the resulting immunoselected CD34+ cells are resuspended in phosphate buffered saline and human serum albumin, thus constituting the final product. ProtheraCytes® are then delivered the next day to the hospital's central pharmacy and transferred to the catheterization laboratory for administration. The purity of CD34+ cells and the content of other cell types such as monocytes, lymphocytes and granulocytes are assessed by flow cytometry to ensure that the final product meets the release specifications.

ProtheraCytes®-associated procedure

The administration procedure may be planned up to 2 months post-AMI. Prior to the transendocardial injection, patients undergo CMR to measure scar thickness and border zone and to confirm the absence of LV thrombus. Other controls include physical examination, an electrocardiogram (ECG), echocardiography staging, troponin I and/or T, NT-pro-BNP/BNP, complete blood count, coagulation factors, hepatic enzymes, adverse events and concomitant treatments. The procedure must be cancelled in the case of a new AMI occurring after randomization, if ProtheraCytes® do not meet release specifications, or if the investigator considers that a discontinuation of the therapy is in the best interest of the patient after review of the CMR performed in the 5 days preceding the procedure.

Procedure for injection

LV transendocardial injections are performed using the Helical™ Infusion (Helix™) Catheter in combination with the Universal Deflectable Guide (Morph®) Catheter (BioCardia, Sunnyvale CA, USA) introduced via the femoral route up to the left ventricle cavity. The Helix™ catheter has a hollow corkscrew-shaped needle telescoped in an 8F Morph steerable guide advanced retrograde through the aortic valve over a guide wire. The needle is rotated clockwise into myocardium for injection and rotated counterclockwise to disengage from the myocardium. Due to its design with a helical needle, the Helix™ catheter remains anchored to the myocardium while the heart is beating, thus reducing the risk of injecting

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Table 1 Exclusion criteria

Current heart diseases or troubles
• Aortic stenosis as determined as valve area less than 1 cm^2 that prohibits catheter access to LV
• Presence of a prosthetic/mechanical aortic or mitral valve or heart constrictive device
• Endocarditis
• Infectious pericarditis
• Pericardial tamponade
• LV thrombus at echocardiography or CMR
• Former or current aortic dissection
• Severe peripheral vascular disease precluding femoral artery access as determined at the time of original catheterization
• Any condition leading to contraindicated or unexploitable CMR
• Takotsubo cardiomyopathy
Heart disease history
• CABG surgery
• Former significant mitral valve replacement surgery or heart transplantation
• Severe valve disease: mitral, aortic stenosis/insufficiency
• Non-ischaemic dilated cardiomyopathy due to valvular dysfunction, mitral regurgitation, tachycardia or myocarditis
Other previous or current conditions
• Conditions requiring previous G-CSF or other haematopoietic growth factor administrations
• Constitutional or acquired coagulopathy
• Active bleeding or major surgery within 1 month
• History of metallic foreign body in their eye
• Malignancies except: non-melanoma skin cancer or adequately treated in situ cervical cancer or previous cancer in complete response without any treatment in the last 5 years
• Mediastinal radiation exposure
• Treated chronic renal failure or haemodialysis or renal severe impairment[a]
• Impairment of cognitive function assessed by Mini Mental State Examination
Previous or current infections
• Sepsis
• Hepatic failure, history of liver cirrhosis or hepatic severe impairment
• History or current human immunodeficiency HIV1-2, HTLV1, HTLV2
• Current active hepatitis B
• History or current Hepatitis C
• Current active syphilis
Other histories
• Splenomegaly
• Phenylketonuria
• Iron-dextran allergy
• Murine protein allergy

[a]Creatinine clearance <30 mL/min.
CABG, coronary artery bypass graft; CMR, cardiac magnetic resonance imaging; G-CSF, granulocyte-colony stimulating factor; HIV, human immunodeficiency virus; HTLV1/2: human T-lymphotropic virus type 1/type2; LV, left ventricle.

Figure 2 Procedure of ProtheraCytes® production and injection. *After randomization and within 45 days after myocardial infarction. CMR, cardiac magnetic resonance.

the cells into the cavity rather than the muscle. The reported rate of transendocardial injection-associated serious adverse events with the Helix™ catheter is low.[22] The injection must be performed in the absence of thrombus in the target area identified at the pre-injection CMR and needs to be compliant with manufacturer's recommendations. The morph catheter tip is positioned towards the targeted tissue under bi-planar fluoroscopic guidance, and the helical infusion catheter is engaged in the myocardium after fluoroscopy has confirmed that the Helix is in the target area perpendicular to the endocardium.

A single one-time administration based on 15 injections (1 mL each) is performed under loco-regional anaesthesia. Due to a possible risk of tamponade, a cardiac echography is performed 1 h after the injection procedure to detect potential pericardial effusion, and a monitoring cardiac

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echography is performed 6 h after injection to check for adverse events. The patients remain hospitalized for 24 h following the injection procedure.

All interventional investigators are trained for the procedure in accordance with the manufacturer recommendations in large animals prior to the first case, and all cases are supported by experienced proctors of field clinical engineers in the technique.

Clinical follow-up

Follow-up assessments are performed at 1, 3 and 6 months, which systematically include physical examination, an echocardiography, the measures of creatinine level and clearance (or estimated glomerular filtration rate), blood cell count, natriuretic peptide level, quality of life with SF36 questionnaires, adverse events and concomitant medications. Assessments at 3 and 6 months also include CMR, an ECG and the assessment of the New York Heart Association (NYHA) functional stage. Single-photon emission computed tomography (SPECT) may be optionally performed at baseline and 6 months.

Outcome measures

The primary endpoint is the 6-month incidence of MACE, defined as the composite incidence of all-cause death, non-fatal recurrent MI or hospitalizations for heart failure (including heart failure-associated urgent visits), non-fatal strokes, other cardiovascular hospitalizations including procedure-associated events leading to hospitalization prolongation (e.g. cardiac tamponade or pericarditis). All endpoint events will be adjudicated and confirmed by an independent and blinded Clinical Events Committee (CEC).

The main secondary endpoints are the improvement of the LV end systolic volume index (LVESVi) and of the viability of infarcted segment(s) from baseline to 6 months. The assessment of the main secondary endpoints as well as other markers such as LVESV, LV end diastolic volume (LVEDV), LVEDV index (LVEDVi), LV mass (LVM), LVM index (LVMi) and LVEF are performed using CMR and perfusion 99mTc SPECT (when available, with viability defined by tracer uptake $>$60%). MVO, an exploratory endpoint, is also assessed at baseline and 6 months.

The number of segments with oedema (high signal intensity area respecting anatomical borders following an expected regional distribution pattern) is visually identified on T2 weighted imaging. Segments with MVO (number of segments according to the 17-segment division of the LV) are identified on late-gadolinium enhancement images, around 10 min after injection. The grade on late gadolinium enhancement for each segment is determined according to a five-grade scale based on the transmural scar extent: 0% = 1, $<$25% = 2, 25%–49% = 3, 50%–75% = 4, $>$75% = 5. The summed hypersignal extension score is determined with the summation of the score of individual segments.[23] The infarct size represents the number of segments with at least 50% of transmurality. All CMRs are reviewed by a centralized blinded Corelab.

Other secondary endpoints include adverse event profile, cardiac event-free survival, median time before cardiac relapse and the quality of life.

Statistical analysis

The statistical analysis of the main outcome consists in the description of the proportion of subjects experiencing at least one adverse event. This proportion is given with its associated exact confidence interval, based on the binomial distribution. MACE incidence is also compared to the assumed MACE proportion of 20% specified in the sample size computation. The proportion of adverse events is also given in the control group. The global significance level (two-sided type I error rate) is set to $\alpha = 0.05$.

Cox model is used for time-to-event data. Repeated data are analysed using linear mixed models with a random subject effect. Time is modelled as a fixed effect and with a time × group interaction. A random time effect is added in a sensitivity analysis. Models are adjusted for baseline values and for patient's age.

The sample size to be analysed has been set to 33 subjects in the ProtheraCytes® arm and 11 in the standard of care arm. This sample size has been chosen considering that the expected proportion of MACE will be low (i.e. lower than 20%). This corresponds to a number of subjects experiencing MACE equal to or lower than six among the 33 subjects in the ProtheraCytes® arm. The width of the exact confidence interval of the matching frequencies (0/33 to 6/33) ranges from 10.6% to 28.5%, which was deemed of sufficient accuracy.

All analyses are conducted on the modified intent-to-treat (mITT) population defined as all patients randomized and for the patients in the ProtheraCytes® arm, those who have received at least one transendocardial injection of ProtheraCytes®. Efficacy analyses are conducted on all mITT patients who have complete evaluable assessments on the endpoints of interest (at baseline and 1, 3 and 6 months post-transplant) and on patients who do not undergo heart transplantation or experience re-MI during the follow-up visit.

Discussion

EXCELLENT is the first endpoint-blinded trial to evaluate the effect of transendocardial injections of expanded autologous CD34+ cells in patients after large AMI and cumulating

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multiple risk factors for developing subsequent heart failure (i.e. elevated troponin levels, LV dysfunction, >50% transmural infarct and akinesia or dyskinesia at CMR).

The manufacturing process allows for the production of high numbers of CD34+ cells, starting from an autologous peripheral blood sample collected after G-CSF mobilization, while potentially avoiding multiple leukapheresis procedures. The biological evaluation of the cell products obtained from healthy donors has shown that after a 9-day expansion process, expanded CD34+ cells, labelled ProtheraCytes®, were identical to non-expanded CD34+ cells in terms of CD34 antigen expression and telomere length.[21] ProtheraCytes® have been shown to secrete pro-angiogenic paracrine factors and differentiate into endothelial cells.[24]

One may expect that the number of cells harvested from AMI patients is dependent on individual variations in cell mobilization capacity due to the smoking status or comorbidities like diabetes mellitus, which are known to have negative impacts on CD34+ cell mobilization by G-CSF.[25,26] In the multivariate analysis of the BONAMI trial including patients with AMI and successful reperfusion, active smoking was significantly correlated with a lower benefit of bone marrow cell (BMC) administration.[10] The StemXpand® manufacturing process of CD34+ cell expansion prior to injection is thereby a major strength of the EXCELLENT trial. Indeed, meta-analyses of studies assessing the effects of progenitor cell delivery in the post-STEMI setting concluded that the strategy was safe, and a benefit on post-infarct cardiac function may be expected if cells were infused in sufficient quantity during the repair phase after STEMI.[27] PreSERVE-AMI is the largest randomized placebo-controlled trial assessing the intracoronary infusion of autologous non-expanded CD34+ cells into post-AMI patients with LVEF <50% after primary PCI.[18] In this trial, CD34+ cells were selected from the harvested cells, and the dose in each subject was the total dose of CD34+ cells produced from their bone marrow aspirate. In the PreSERVE-AMI trial, the mean CD34+ cell count in the final cell product was 15 ± 8 million cells. The results showed that the treatment decreased mortality and MACE incidence compared to the placebo control arm at 1-year follow-up and that the LVEF change was significantly greater than in the control group in those receiving CD34+ cell doses >20 million cells. The dose-dependent effect observed in this trial, which was consistent with what had been shown in the phase 1 trial,[17] supports the need for a technology that allows for the expansion of CD34+ cells to increase the odds of a meaningful clinical efficacy.

The cell therapy in the EXCELLENT trial is delivered through the transendocardial injection route. This is another important advantage of the EXCELLENT trial compared to studies using intracoronary delivery. A meta-analysis based on 149 selected studies concluded that the benefit of intracoronary cell therapy after AMI is poor regarding clinical events or changes in LV function.[28] While being possibly biased by the combination of several different cell types used, this analysis is in favour of alternative cell administration methods. A randomized study performed in patients with dilated cardiomyopathy (DCM) showed that transendocardial CD34+ cell transplantation was associated with significantly higher myocardial retention rates 18 h after the procedure when compared to intracoronary transplantation (19.2 ± 4.8% vs. 4.4 ± 1.2%, $P < 0.01$) and a greater improvement at 6 months of LV function, NT-pro-BNP and exercise capacity compared with the intracoronary route.[20] While post-MI myocardium is expected to be less robust than fibrosed DCM ventricle, which may limit extrapolation to the EXCELLENT trial, several preclinical studies highlighted the interest of injecting stem cells transendocardially.[29,30] A study performed in swine showed that the ^{18}fluorodeoxyglucose-labelled cell delivery using a transendocardial helical infusion delivery system was more efficient than either transepicardial injection or intracoronary infusion. It was postulated that the transendocardial delivery system has the potential to improve local cell delivery and retention.[30] The safety and benefits of transendocardial stem cell injections in patients with LV dysfunction due to ischemic cardiomyopathy (ICM) were shown in the phase 1/2 POSEIDON trial[31] and supported by a meta-analysis based on 20 randomized clinical trials in patients undergoing coronary artery bypass grafting (CABG).[32] It was found that intramyocardial cell administration during CABG improved cardiac function with no significant risk difference when compared to CABG alone. Transendocardial administration of cells has better retention rates compared to intracoronary infusion that can potentially lead to a more efficient tissue repair through the secretion of paracrine factors that induce neovascularization, reduced fibrosis and apoptosis, and recruitment of additional stem/progenitor cells.[33]

The main limitation of the transendocardial approach is the presence of LV thrombus formation that is expected to occur in 9% and 14% of patients without or with anterior AMI, respectively.[34] LV thrombus is a well-known complication of AMI and a strict contraindication to the transendocardial approach due to the risk of systemic arterial embolism. In the EXCELLENT trial, all patients undergo CMR before injection to check for a LV thrombus and, if any, are withdrawn from the trial.

The EXCELLENT phase 1/2b trial is aimed at assessing the feasibility and safety of transendocardial injections of ProtheraCytes® in post-AMI patients, including elderly, and their preliminary impact on MACE over 6-month follow-up. LVESVi was selected as a surrogate criterion of efficacy based on its significance in patients with previous MI and LV remodelling. A study in 450 patients with ICM (≥70% stenosis in ≥1 epicardial coronary artery) reported that the interaction between scar percentage and LVESVi, and the interaction between post-revascularization and LVESVi, were independently associated with mortality.[35] The relevance of this parameter is also supported by reviews and analyses on the association

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of autologous BMC infusion and the improvement of LV systolic function and remodelling in patients after STEMI.[34,36] In particular, the improvements in LVEF, scar size and LVESV were similar when BMC injections were performed within 7 days or between 7 and 30 days after AMI and/or PCI. The improvement in LVEDV was also significant when cells were injected within 7 days. However, when BMC injection was made between 7 and 30 days, it failed to reduce LVEDV.[37] This last point supported the choice for LVESVi as an efficacy endpoint in the EXCELLENT trial as the cells are injected within 2 months after AMI. The EXCELLENT trial will also provide the opportunity to assess the benefits of transendocardial injection of expanded CD34+ cells in patients with MVO. Indeed, the analysis of four randomized clinical trials including patients with STEMI receiving BMCs indicates that MVO at baseline is associated with a significantly greater recovery of LVEF.[37] The exploratory evaluation of the results of the EXCELLENT trial could be of great interest for the design of further trials given that MVO is significantly and independently associated with all-cause mortality and is more predictive of MACE than infarct size,[38] so this subgroup of patients may particularly benefit from stem cell therapy.

The limitations of the EXCELLENT trial will be discussed in the light of the results. The methodological approach is consistent with the objectives of the study, that is, the validation of the feasibility and safety of transendocardial injections, and the identification of congruent favourable endpoints that would warrant a larger randomized clinical trial in comparison with a standard of care alone. A possible comparison to a placebo control arm, not retained in EXCELLENT for both methodological and ethical reasons, will have to be discussed.

In summary, the secondary prevention of heart failure and its consequences after AMI are still a major challenge. Autologous transplantation of CD34+ cells is an attractive option supported by preclinical and clinical studies but is currently limited by technological constraints regarding the numbers of cells to be injected and the route of injection. EXCELLENT is the first clinical trial that will evaluate the effect of CD34+ cells expanded with an automated manufacturing process and administered transendocardially, two key factors expected to optimize the CD34+ cell-based therapy in the post-AMI setting.

Acknowledgements

The authors wish to thank Hervé Bismut (Geminicis, Paris) for his help in writing, editorial support and formatting assistance that was funded by CellProthera and Dr Ibon Garitaonandia (CellProthera) for helpful scientific discussions during the preparation of the manuscript.

Conflict of interest

DLB discloses the following relationships: Advisory Board: Angiowave, Bayer, Boehringer Ingelheim, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Stasys; Board of Directors: American Heart Association New York City, Angiowave (stock options), Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock); Consultant: Broadview Ventures, GlaxoSmithKline, Hims, SFJ, Youngene; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic, Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical; for ALLAY-HF, funded by Alleviant Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), CSL Behring (AHA lecture), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), WebMD (CME steering committees), Wiley (steering committee); Other: Clinical Cardiology (Deputy Editor); Patent: Sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon; neither I nor Brigham and Women's Hospital receive any income from this patent); Research Funding: Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Alnylam, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers

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Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CinCor, Cleerly, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Otsuka, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, Youngene, 89Bio; Royalties: Elsevier (Editor, Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St. Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, Vascular Solutions; Trustee: American College of Cardiology; Unfunded Research: FlowCo. JR has been an advisory board member and has received consulting fees from CellProthera. FZ reports personal fees from Applied Therapeutics, Bayer, Biopeutics, Boehringer Ingelheim, Bristol-Myers Squibb, CVRx, Cardior, Cereno pharmaceutical, CellProthera, Merck, Northsea, Novartis, NovoNordisk, Otsuka and Owkin, having stock options at G3Pharmaceutical and equities at Cereno pharmaceutical, Cardiorenal and Eshmoun Clinical research and being the founder of Cardiovascular Clinical Trialists (CVCT). JR, PYM, DLB, SDS, GM and FZ received fees from CellProthera as members of the steering committee of the EXCELLENT trial. GT and MdK are staff members of CellProthera. Other authors declared no conflicts of interest.

Funding

The EXCELLENT trial is sponsored by CellProthera.

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