Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial

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Summary

Background Ixmyelocel-T is an expanded, multicellular therapy produced from a patient's own bone marrow by selectively expanding two key types of bone marrow mononuclear cells: CD90+ mesenchymal stem cells and CD45+ CD14+ auto-fluorescent+ activated macrophages. Early phase clinical trials suggest that intramyocardial delivery of ixmyelocel-T might improve clinical, functional, symptomatic, and quality-of-life outcomes in patients with heart failure due to ischaemic dilated cardiomyopathy. We aimed to assess the safety and efficacy of catheter-based transendocardial injection of ixmyelocel-T cell therapy in patients with heart failure and reduced ejection fractions.

Methods In this randomised, double-blind, placebo-controlled phase 2B trial (ixCELL-DCM), patients from 31 sites in North America with New York Heart Association class III or IV symptomatic heart failure due to ischaemic dilated cardiomyopathy, who had left ventricular ejection fraction 35% or less, an automatic implantable cardioverter defibrillator, and who were ineligible for revascularisation procedures were randomly assigned (1:1) to receive ixmyelocel-T or placebo at the time of bone marrow aspiration and followed for 12 months. Randomisation was done through an interactive (voice/web) response system. The pharmacist, treating physician, and coordinator at each site were unblinded, but the the follow-up team was completely blinded. The primary endpoint was a composite of all-cause death, cardiovascular admission to hospital, and unplanned clinic visits to treat acute decompensated heart failure based on the blinded adjudication of an independent clinical endpoint committee. Primary efficacy endpoint analyses and safety analyses were done by modified intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01670981.

Findings Between April 2, 2013, and Jan 28, 2015, 126 participants were randomly assigned to receive either ixmyelocel-T (n=66) or placebo (n=60). 114 (90%) patients comprised the modified intention-to-treat population and 109 (87%) patients were included in the per-protocol primary efficacy analysis (58 in the ixmyelocel-T group and 51 in the placebo group). The primary efficacy endpoint was observed in 47 patients: 50 events in 25 (49%) of 51 patients in the placebo group and 38 events in 22 (38%) of 58 patients in the ixmyelocel-T group, which represents a 37% reduction in cardiac events compared with placebo (risk ratio 0·63 [95% CI 0·42–0·97]; p=0·0344). 41 (75%) of 51 participants in the placebo group had serious adverse events versus 31 (53%) of 58 in the ixmyelocel-T group (p=0·0197).

Interpretation To the best of our knowledge, ixCELL-DCM is the largest cell therapy study done in patients with heart failure so far. The transendocardial delivery of ixmyelocel-T in patients with heart failure and reduced ejection fraction due to ischaemic dilated cardiomyopathy resulted in a significant reduction in adjudicated clinical cardiac events compared with placebo leading to improved patient outcomes.

Funding Vericel Corporation.

Introduction

Coronary heart disease often leads to ischaemic dilated cardiomyopathy and progressive congestive heart failure. Ischaemic dilated cardiomyopathy is one of the leading causes of morbidity and mortality as well as the largest cause of hospital readmissions in the USA.[1–3] This progressive deterioration of cardiac performance is due, in part, to cumulative myocyte loss and the absence of regenerative capacity in mature, differentiated mammalian myocardium.[4] Despite advances in medical treatment, ventricular device therapy and heart transplantation are often used, although the number of available organs is limited and both procedures have associated complications and costs.[5,6] Identification and characterisation of an effective biological therapy for myocardial repair is one of the highest priorities to advance the treatment and prevention of ischaemic dilated cardiomyopathy. First-generation autologous cell therapies to treat ischaemic dilated cardiomyopathy have had limited benefit, potentially because of cell composition, variability of cell potency related to ageing and medical comorbidities along with the absence of ability to reduce existing scar tissue, or modest reproducibility due to lack of defined cell types or doses.[7–13] We chose to use ixmyelocel-T to address a number of these issues because it has the potential positive properties of mesenchymal stem cells (MSCs) as well as the potential positive remodelling and

Research in context

Evidence before the study

Patients with New York Heart Association class III/IV symptoms, despite optimal medical and device therapy, have few options beyond heart transplantation and left ventricular assist device therapy. Cell therapy represents a novel approach to these patients. The heart has restricted regenerative capacity and the hope is that stem therapy will enhance the natural process of the regeneration and remodelling of scar tissue. Successful results in a range of preclinical models with a wide variety of cells were reported in early clinical trials. A recent meta-analysis reported on 31 clinical trials with 1521 randomised participants including 882 treated with cell therapy and 639 with placebo or control. Substantial heterogeneity exists in the trials, which are generally small and many were not randomised or double blind. Most trials used unselected autologous bone marrow cells with the advantage of availability and simplicity but the major limitation being variability in the cell product based on the fact that stem cell number and potency decline with age and cardiovascular risk factors. The results of the meta-analysis were encouraging with excellent safety and modest improvement in left ventricular ejection fraction (LVEF), exercise capacity, and quality of life, and suggests a reduction in the risk of mortality and admissions to hospital due to heart failure.

Approaches to improve on the use of autologous bone marrow include allogeneic stem cells, selected cells (CD34+, adipose derived, mesenchymal stem cell), or cardiac derived cells. Another approach has been to augment or enhance the autologous cells. Ixmyelocel-T is an expanded multicellular therapy produced from autologous bone marrow by selectively expanding two key types of bone marrow mononuclear cells: CD90+ MSC and CD45+ CD14+ activated macrophages. This expanded product was tested in two previous heart failure trials: IMPACT-DCM and CATHETER-DCM in 21 patients with ischaemic dilated cardiomyopathy and 18 with non-ischaemic dilated cardiomyopathy. These results showed that percutaneous catheter based delivery was associated with fewer procedure related events than a surgical approach and patients with ischaemic dilated cardiomyopathy had a reduction in major adverse cardiovascular events, improvements in NYHA class symptoms, and the 6 min walk test. These results provided the support for the phase 2 randomised double-blind ixCELL-DCM study.

Added value of this study

To the best of our knowledge, ixCELL-DCM is the largest randomised double-blind placebo-controlled trial to be published. The results of both the per-protocol (n=109) and the modified intention-to-treat (n=114) populations indicate that patients given ixmyelocel-T had a reduction in the primary endpoint, which was a composite of all-cause death, cardiovascular admission to hospital, and unplanned clinic visits to treat acute decompensated heart failure. The secondary endpoint of LVEF measured by echocardiography showed only minor improvements in LVEF and LV volumes, which were numerically higher in the cell treated group but did not differ significantly from the placebo group. Both groups had an improvement in the 6 min walk test with no statistical difference between groups. These results confirm the benefit of intramyocardial delivered ixmyelocel-T observed in the earlier open-label studies for the improvement of clinical outcomes in patients with ischaemic dilated cardiomyopathy.

Implications of all available evidence

The results of the ixCELL-DCM trial add to the available evidence that cell therapy is a promising treatment for patients with ischaemic heart failure based on a reduction in all-cause mortality and cardiovascular admissions to hospital. The improvements in clinical events seem to be more significant than the improvements in left ventricular function and therefore more studies are necessary to determine the mechanism of benefit for this therapy. Finally, these results should stimulate additional cell therapy trials to further explore the benefit of cell therapy in patients with heart failure.

anti-inflammatory capabilities of the M2 macrophages.[14–16] ixmyelocel-T is a single expanded product that contains the same mixture of cell types found in the bone marrow mononuclear cell population, but about 200 times the number of M2 macrophages and 50 times the number of CD90+ MSCs. Because it is a mixed-cell therapy, ixmyelocel-T is believed to have a wider range of biological activities than does a single-cell therapy. Preclinical studies have shown that the biological activities of ixmyelocel-T include tissue remodelling, immunomodulation, angiogenesis, and endothelial protection.[14–16] The exact mechanism remains unknown but is likely a multicellular effect.

The use of ixmyelocel-T to treat congestive heart failure caused by ischaemic dilated cardiomyopathy is based on data from the open-label phase 2A trials IMPACT-DCM and CATHETER-DCM, which examined the safety and efficacy of intramyocardial injection of ixmyelocel-T in patients with ischaemic or non-ischaemic dilated cardiomyopathy (DCM) compared with a standard of care control group.[17] Ixmyelocel-T was injected into the myocardium via thoracotomy or thoracoscopy in IMPACT-DCM and via NOGA MyoStar catheter transendocardial injections in CATHETER-DCM. In pooled data from the two trials, 21 patients with ischaemic dilated cardiomyopathy and 18 with non-ischaemic ischaemic dilated cardiomyopathy were given ixmyelocel-T. Significantly more adverse events were noted when ixmyelocel-T was given via surgery compared with catheter-based transendocardial administration. Among patients with ischaemic dilated cardiomyopathy, treatment with ixmyelocel-T was associated with fewer

major adverse cardiovascular events (MACE) and improvement in New York Heart Association (NYHA) class, 6 min walk test (6MWT) distance, and Minnesota Living with HF Questionnaire (MLHFQ). Such benefits were not observed in the patients with non-ischaemic dilated cardiomyopathy.[17]

Therefore, we aimed to assess the efficacy and safety of ixmyelocel-T injected transendocardially into patients with congestive heart failure due to ischaemic dilated cardiomyopathy compared with placebo.[14–18]

Methods

Study design and participants

This phase 2b, randomised, double-blind, placebo-controlled, parallel-group multicentre trial (ixCELL-DCM) was done at 31 sites in North America that began screening patients in February, 2013.[18] The last patient 12-month follow-up was done in February, 2016. The full details of the inclusion and exclusion criteria have been previously published.[18] Briefly, the trial enrolled adults (aged 30–86 years) with symptomatic NYHA class III or IV heart failure due to ischaemic dilated cardiomyopathy, with left ventricular ejection fraction (LVEF) 35% or less, who had been implanted with an automatic implantable cardioverter defibrillator (AICD) but were ineligible for revascularisation procedures.

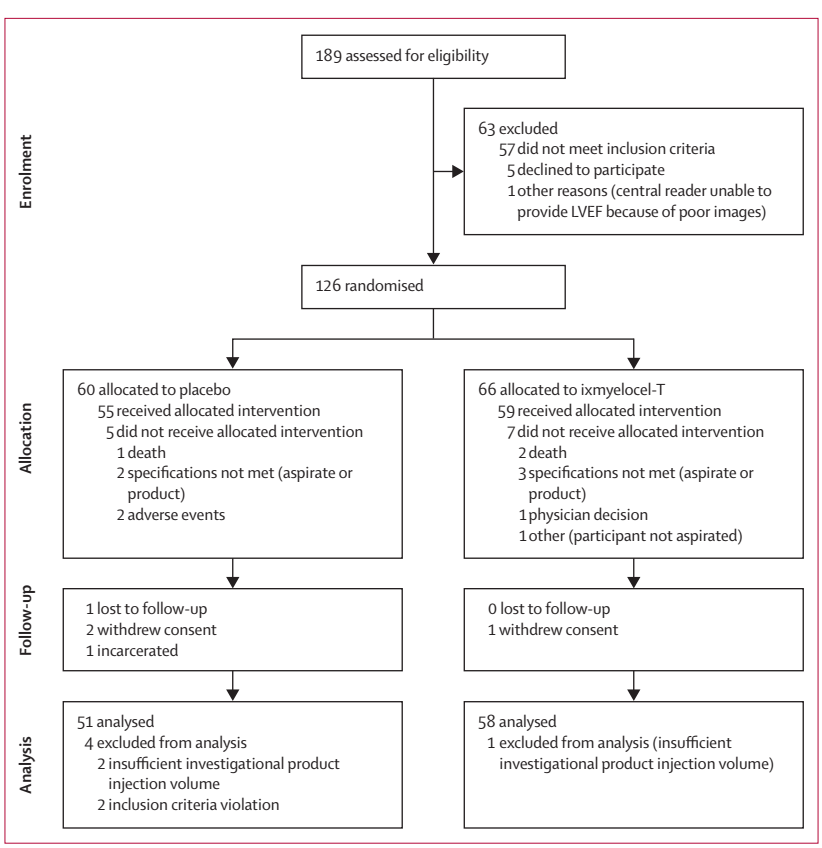


Figure 1: **Trial profile**
LVEF=left ventricular ejection fraction.

The trial was conducted under a US FDA Investigational New Drug (IND) in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and was approved by the Investigational Review Board at each participating clinical site. All study participants provided written informed consent before study entry.

Randomisation and masking

Patients who met eligibility criteria were randomly assigned (1:1) to receive either ixmyelocel-T or placebo (vehicle control), with randomisation stratified by study site. Randomisation was done through an interactive (voice/web) response system. All patients were masked to the treatment and received endocardial mapping and injections. Investigators were also masked including a second team used for follow-up assessments that was not involved in the injection procedure. The treating physician and coordinator at each site were unblinded.

Procedures

All randomised patients, including those assigned to placebo, underwent a percutaneous, small volume (~60 mL) bone marrow aspiration from the posterior iliac crest under appropriate anaesthesia. Bone marrow aspirate was shipped overnight to a manufacturing facility (Vericel Corp [formerly Aastrom Biosciences], Ann Arbor, MI, USA) and ixmyelocel-T was prepared and the final product was shipped to sites as previously described.[14–17] A vehicle control composed of the same excipients as used in ixmyelocel-T was prepared for all patients in the placebo group at the manufacturing facility. Pharmacists (or other designated study personnel) loaded 0·8 mL of the final product into 1 mL syringes, allowing two 0·4 mL injections per syringe. Ixmyelocel-T and placebo have different physical characteristics, which might be evident to study personnel who handle the shipped product or syringes. Therefore, study personnel who prepared the syringes, and the physician and any assistant(s) involved in administering injections, were not allowed to perform follow-up procedures or assessments of study patients after injection. A separate team of study personnel performed all post-injection follow-up safety and efficacy assessments.

About 15 days after bone marrow aspiration, cardiac mapping and transendocardial injections of Ixmeylocel-T or placebo were done with the NOGA XP Cardiac Navigation System (Biosense Webster, Diamond Bar, CA, USA), by investigators with certified training.[17] Patients were prepared for cardiac catheterisation according to each site's standard procedures. Using the NOGASTAR catheter, a series of individual points were recorded and tracked to generate a three-dimensional electromechanical map of the left ventricular inner contours, identifying the border zone of viable and non-viable myocardium based on voltage maps as previously described.[17,18] Then the MYOSTAR injection catheter was used to inject either ixmyelocel-T or placebo into selected target tissue.[17] The

	Placebo (n=51)	Ixmyelocel-T (n=58)
Sex		
Male	45 (88·2)	55 (94·8)
Female	6 (11·8)	3 (5·2)
Age (years)	64·7 (9·94)	65·3 (8·49)
Ethnic origin		
White	45 (88%)	53 (91%)
Black or African American	5 (10%)	1 (2%)
American Indian or Alaska Native	1 (2%)	1 (2%)
Other	0	3 (5%)
Body-mass index (kg/m²)	30·7 (4·99)	29·9 (3·95)
Cigarette use		
Current user	4 (8%)	3 (5%)
Former user	31 (61%)	40 (69%)
Never used	16 (31%)	15 (26%)
Alcohol use		
Current user	16 (31%)	28 (48%)
Former user	20 (39%)	19 (33%)
Never used	15 (29%)	11 (19%)
Serum creatinine (mg/dL)	1·2 (0·46)	1·3 (0·51)
Creatinine clearance (mL per min/m²)	61·9 (19·04)	61·8 (21·37)
Systolic blood pressure (mm Hg)	126·0 (18·51)	120·3 (18·72)
Diastolic blood pressure (mm Hg)	74·2 (11·05)	70·5 (10·53)
Left ventricular ejection fraction (%)	24·4% (6·0)	26·5% (5·1)
6-min walk test (m)	302 (105)	313 (100)
NT-ProBNP (ng/L)	2132 (2021)	1755 (1842)
NYHA stage of heart failure		
I	0	0
II	2 (4%)	2 (3%)
III	47 (92%)	52 (90%)
IV	2 (4%)	4 (7%)
(Table 1 continues in next column)		
(Continued from previous column)		
Canadian Cardiovascular Society class		
I	7 (14%)	4 (7%)
II	6 (12%)	6 (10%)
III	9 (18%)	7 (12%)
IV	1 (2%)	1 (2%)
No angina	26 (51%)	38 (66%)
Cardiovascular medical history		
Myocardial infarction	49 (96%)	51 (88%)
Angina pectoris	32 (63%)	31 (43%)
Hypertension	46 (90%)	47 (81%)
Hypercholesterolaemia	49 (96%)	56 (97%)
Hypertriglyceridaemia	22 (43%)	16 (28%)
Cerebrovascular accident/stroke	11 (22%)	9 (16%)
Diabetes mellitus	26 (51%)	24 (41%)
Peripheral artery disease	7 (14%)	11 (19%)
PTCA	42 (82%)	49 (85%)
CABG	32 (63%)	32 (55%)
AICD	49 (96%)	54 (93%)
CRT	20 (39%)	29 (50%)
Concomitant medications		
ACE inhibitor	34 (67%)	32 (55%)
Antiplatelet therapy	48 (94%)	53 (91%)
β blocker	48 (94%)	58 (100%)
Diuretic	50 (98%)	55 (94%)
Statin	46 (90%)	56 (97%)
Warfarin	14 (27%)	16 (28%)

Data are n (%) or mean (SD). NYHA= New York Heart Association. PTCA=percutaneous transluminal coronary angioplasty. CABG=coronary artery bypass grafting. AICD=automatic implantable cardioverter defibrillator. CRT=cardiac resynchronisation therapy. ACE=angiotensin converting enzyme.

Table 1: **Patient demographics**

injection procedure was terminated if at any time the patient experienced a serious adverse event. A post-injection transthoracic echocardiogram was done to look for new effusions or structural abnormalities and the patients were admitted to hospital overnight to monitor haemodynamics and safety parameters.

All imaging analysis was done by an independent core laboratory (ICON Medical Imaging; Warrington, PA, USA).

Outcomes

The primary efficacy endpoint was a composite of the total number of clinical cardiac events as defined by all-cause deaths, cardiovascular admissions to hospital, or unplanned outpatient and emergency departments visits to treat acutely decompensated heart failure during the 12 months after administration of study treatment, excluding events considered to be related to the catheterisation or injection procedure that occurred within 7 days of treatment. We assessed a number of secondary outcomes; the win ratio (analysis of all cause deaths, cardiovascular admissions to hospital, and emergency department/outpatient visits to treat acutely decompensated coronary heart failure), LVEF, LVESV, LVEDV, LV stroke volume, NYHA class (reported here), wall motion index by echocardiogram, Minnesota living with heart failure questionnaire, EuroQual-5D summary index, ventricular arrhythmia episodes, and total number of days hospitalised, change from baseline in NT-proBNP, albumin/creatinine ratio, high sensitivity C-reactive protein, troponin I, creatinine, and uric acid (not reported here). Exploratory endpoints include medical resource utilisation and mitral valve regurgitation (not reported here).[19,20] Follow-up evaluations of all patients were done at 1, 3, 6, and 12 months. All

	Primary endpoint without investigational product procedure related events		Sensitivity endpoint with investigational product procedure related events	
	Placebo (n=51)	Ixmyelocel-T (n=58)	Placebo (n=51)	Ixmyelocel-T (n=58)
Rate ratio (95% CI)	..	0·63 (0·42–0·97)	..	0·62 (0·41–0·95)
p value	..	0·0344	..	0·0267
Events per 100 patient-years	109·97	69·76	112·17	69·76
Patient-years exposed	45·5	54·5	45·5	54·5
Total events	50	38	51	38
Distribution of events by patient				
0	26 (51%)	36 (62%)	25 (49%)	36 (62%)
≥1	25 (49%)	22 (38%)	26 (51%)	22 (38%)
1	9 (18%)	13 (22%)	10 (20%)	13 (22%)
2	11 (22%)	3 (5%)	11 (22%)	3 (5%)
3	2 (4%)	5 (9%)	2 (4%)	5 (9%)
4	2 (4%)	1 (2%)	2 (4%)	1 (2%)
5	1 (2%)	0	1 (2%)	0
Death (n patients)	7 (14%)	2 (3%)	..	..
LVAD insertion (n patients)	0	3 (5%)	..	..
Heart transplant (n patients)	1 (2%)	1 (2%)	..	..
Cardiovascular admissions to hospital (n patients)	24 (47%)	22 (38%)	..	..
Unplanned outpatient or emergency department visit (n patients)	0	2 (3%)	..	..

LVAD=left ventricular assist device.

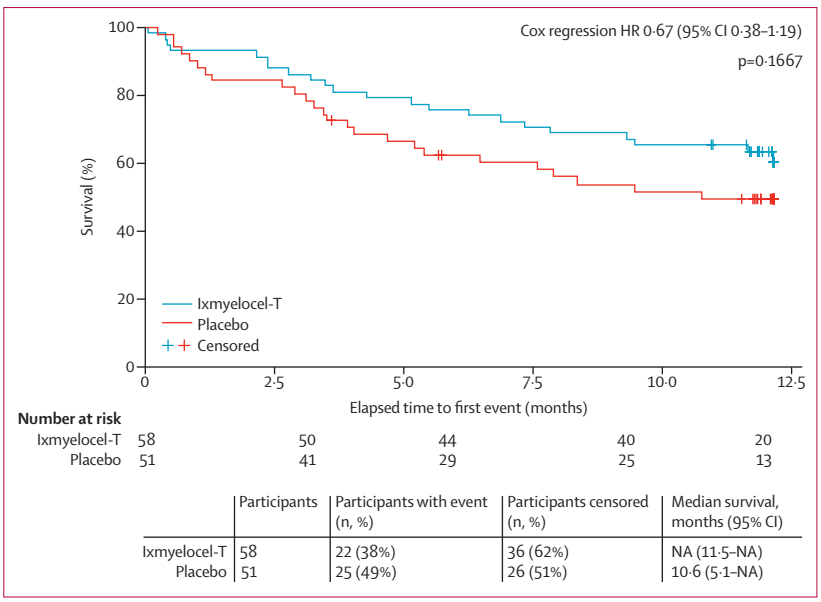
Table 2: **Primary endpoint**

	Placebo (n=51)	Ixmyelocel-T (n=58)
Incidence of individual components*		
All-cause deaths/LVAD/heart transplants	8/51 (16%)	6/58 (10%)
Death	7/51 (14%)	4/58 (7%)*
LVAD insertion	0/51	3/58 (5%)
Heart transplant	1/51 (2%)	1/58 (2%)
Cardiovascular admission to hospital (events n)	42	30
Unplanned outpatient or emergency department visits to treat ADCHF (events)	0	2
Pair categorisation and win ratio†		
Death/LVAD implant/heart transplant on ixmyelocel-T first (a)	271	..
Death/LVAD implant/heart transplant on placebo first (b)	438	..
Cardiovascular admission to hospital on ixmyelocel-T first (c)	504	..
Cardiovascular admission to hospital on placebo first (d)	770	..
Unplanned outpatient or emergency department Intervention for ADCHF on ixmyelocel-T first (e)	0	..
Unplanned outpatient or emergency department intervention for ADCHF on placebo first (f)	0	..
None of the above (g)	975	..
NW: pairs where ixmyelocel-T wins (b + d + f)	1208	..
NL: pairs where placebo wins (a + c + e)	775	..
Win ratio (NW/NL) [95% CI]	1·56 [0·87–2·81]	..
p value	0·1391	..

Data are n/N (%). Composite weighted all-cause deaths/LVAD/heart transplants, cardiovascular admissions to hospital, or unplanned outpatient or emergency departments visits for treatment of ADCHF. Irrespective of the timing, a single event in the primary endpoint analysis could have several components for comparison in this analysis. For example, for a patient first admitted to hospital for a cardiovascular reason who dies while in hospital, the primary analysis counts this as a single event (death) but for the win ratio both the date of death and the date of cardiovascular admission to hospital are used as components for pair categorisation. ADCHF=acutely decompensated congestive heart failure. LVAD=left ventricular assist device. *The four deaths in the ixmyelocel-T group include two patients who had an LVAD implanted and died following the implant. Deaths after LVAD implantation or heart transplant were not counted as separate events. †All pairs: control to ixmyelocel-T (n=2958).

Table 3: **Secondary endpoint—win ratio**

admissions to hospital, outpatient or emergency department visits, and deaths that occurred after treatment were documented. For each event, the underlying cause, any available clinical diagnostic information, and management was recorded by the site investigator or blinded clinician, or both. All endpoint events were adjudicated according to standard definitions in a blinded fashion by an independent adjudication committee. An additional independent Data and Safety Monitoring Board periodically reviewed unblinded safety data throughout the trial. Safety monitoring included aspiration site assessments, percutaneous catheter site assessments, post-catheterisation monitoring, adverse events, vital signs, concomitant medications, physical examinations, immune response results analysing for the presence of antibovine and antiequine antibodies, and clinical laboratory results. Data not shown include aspiration site assessments, percutaneous catheter site assessments, post-catheterisation monitoring, vital signs, concomitant medications, physical examinations, immune response results analysing for the presence of antibovine and entiequine antibodies, and clinical laboratory result.



	Participants	Participants with event (n, %)	Participants censored (n, %)	Median survival, months (95% CI)
Ixmyelocel-T	58	22 (38%)	36 (62%)	NA (11·5–NA)
Placebo	51	25 (49%)	26 (51%)	10·6 (5·1–NA)

Figure 2: **Kaplan-Meier analysis of time to first occurence of primary endpoint event for ixmyelocel-T versus placebo (n=109)**
NA=not applicable.

Statistical analysis

The prespecified primary endpoint compared the total number of clinical events in the ixmyelocel-T group with those in the placebo group 12 months after injection, using Poisson regression to estimate the incidence rate ratio. The primary endpoint analysis was protocol driven as determined by having at least five investigational product syringes (with a total volume of 0·8 mL per syringe) having to be prepared for injection, and that the patient had to have received at least 50% of the total volume of investigational product or not having a protocol violation (n=109), and not based on modified intention to treat as defined by all patients who received the investigational product (n=114). A sample size of about 114 patients (randomised 1:1 to ixmyelocel-T or placebo) provided 82% power to detect a treatment difference at a two-sided 0·05 significance level (assuming event rates per patient-year of 1·3 with placebo and 0·7 with ixmyelocel-T). Events considered related to catheterisation or injection procedure that occurred within 7 days of treatment were not to be counted in the primary analysis. However, a sensitivity analysis including events related to the catheterisation or injection procedure was done. All efficacy analyses used a two-sided 0·05 significance level and were done on the full analysis set, defined as on-treatment analysis of patients who were randomised, aspirated, and received all planned injections of their randomised treatment. The components of the primary endpoint were also analysed with using the win ratio in a hierarchical manner using the method of Pocock and colleagues to incorporate both the incidence and timing of the endpoint components.[19] Secondary efficacy endpoints were analysed similarly to the primary endpoint, but included events considered related to catheterisation or treatment administration. Secondary efficacy endpoints related to change from baseline were analysed with analysis of covariance, with treatment as a factor and the baseline value as a covariate, to determine least squares means (LSM), differences in LSMs compared with placebo, and 95% CIs. If the specified assessment data were missing, the last non-missing, post-baseline assessment was carried forward. Secondary endpoints relating to time to events were summarised with Kaplan-Meier cardiac event curves and analysed with a log-rank and Cox proportional hazards model to determine the hazard ratio (95% CI) and p value. Adverse events were summarised by organ system class, severity, relationship to investigational product and injection procedure, and by treatment group. MACE were predefined as unstable angina requiring admission to hospital, myocardial infarction, stroke, worsening congestive heart failure requiring admission to hospital, ventricular assist device implantation, heart transplant, resuscitated sudden death, defined as successful resuscitation from sudden death or cardiac death, or patients receiving a successful appropriate shock for ventricular arrhythmia in association with loss of consciousness or cardiovascular death. The incidence of MACE was determined in the safety population per the prespecified analysis plan and was not adjudicated. The primary endpoint went through the blinded adjudication process.

Data were analysed with SAS version 9.3.

This study is registered with ClinicalTrials.gov, number NCT01670981.

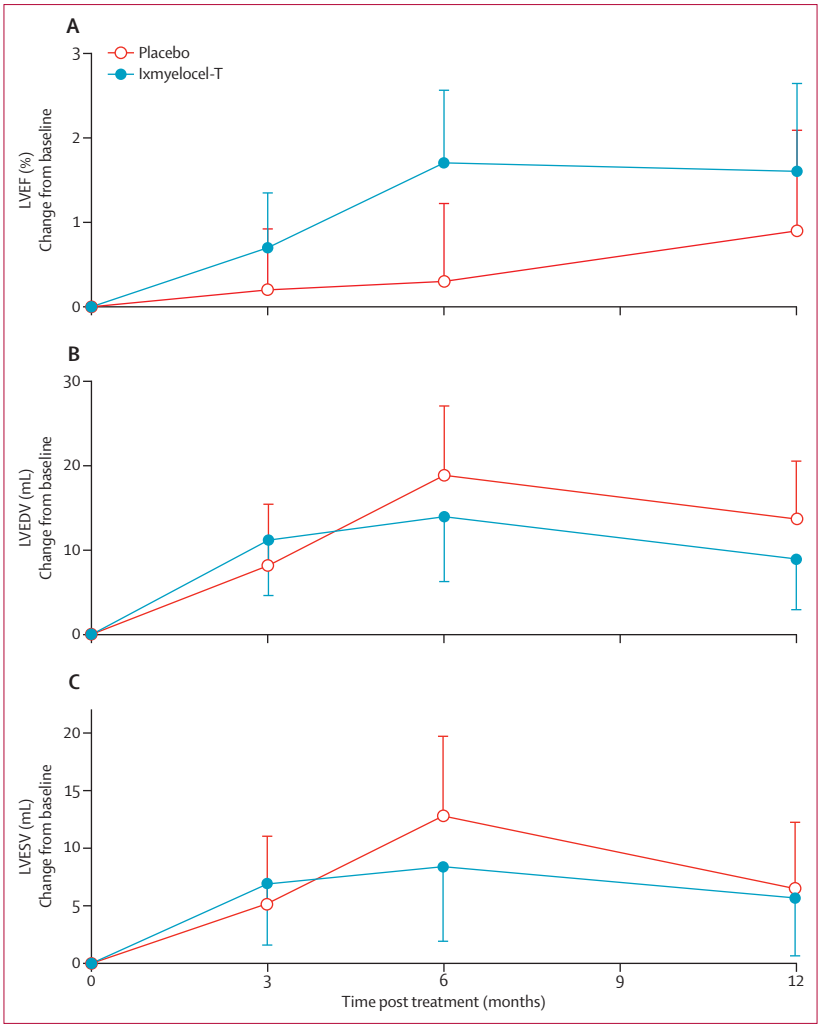


Figure 3: **Structural changes**
Data are mean, error bars show SEM. Left ventricular function (LVEF) change from baseline (A), change from baseline in left ventricular end diastolic volume (LVEDV; B), and change from baseline in left ventricular end systolic volume (LVESV; C). 47, 46, 43, and 37 patients in the placebo group provided data at baseline, month 3, 6, and 12, respectively, for each of these endpoints. 58, 56, 49, and 48 patients in the ixmyelocel-T group provided data at baseline, month 3, 6, and 12, respectively, for each of these endpoints.

Role of the funding source

The trial including patient management, data collection, and data analysis, was funded by Vericel Corporation. Vericel was involved in designing the study and in data analysis. They also contributed to data interpretation and writing of the report. The corresponding author had full access to all data in the study and, with the support of the full author group, had final responsibility for the decision to submit for publication.

Results

Between April 2, 2013, and Jan 28, 2015, 126 participants were randomly assigned to receive either ixmyelocel-T (n=66) or placebo (n=60). 114 patients were given treatment and available for the modified intention-to-treat (ITT) analysis (appendix pp 1–2) and with 109 included for per-protocol specified analysis (51 in the placebo group and 58 in the ixmyelocel-T group; figure 1). The specific details for a patient not undergoing treatment are shown in figure 1. During the 12 month follow-up, 12 patients died (eight in the placebo group and four in the ixmyelocel-T group) and five patients were discontinued from the study. Reasons for discontinuation included withdrawal by participant (two in the placebo group and one in the ixmyelocel-T group), lost to follow-up (one in the placebo group), and other (one incarceration in the placebo group). Baseline characteristics were well balanced between the two treatment groups (table 1). 114 patients were injected with either ixmyelocel-T or placebo. Per protocol, a volume of about 5·8–8·4 mL was delivered as a series of 12–17 injections of 0·4 mL each until all the product was administered. The patients who did not receive "adequate" injections received either 3·2 mL, 2·05 mL, or 1·85 mL of product corresponding to a total of eight, six, or five injections, respectively.

The primary efficacy endpoint was observed in 47 patients: 50 events in 25 (49%) of 51 patients in the placebo group and 38 events in 22 (38%) of 58 patients in the ixmyelocel-T group. Analysis showed that patients who received ixmyelocel-T had a 37% reduction in cardiac events compared with the placebo group (Poisson regression rate ratio 0·63 [95% CI 0·42–0·97]; p=0·0344; table 2). All but one deaths were adjudicated to be cardiovascular as to the cause. Sensitivity analysis including catheterisation or injection procedure related events also favoured ixmyelocel-T over placebo (Poisson regression rate ratio 0·62 [95% CI 0·41–0·95]; p=0·0267).

One of the secondary endpoints, the win ratio, showed that more often ixmyelocel-T (1208 patient pairs) versus placebo (775 patient pairs) was the so-called winner, but this difference did not reach statistical significance (p=0·1391; table 3). The secondary endpoint of time to first clinical cardiovascular event of ixmyelocel-T versus placebo showed a non-significant reduction in events in the treatment group (Cox regression HR 0·67 [95% CI 0·38–1·19]; p=0·1667; figure 2).

Overall, no significant structural changes in left ventricular cavity size as measured by left ventricular end systolic volume (LVESV) and left ventricular end diastolic volume (LVEDV) or LVEF were noted in either the ixmyelocel-T or placebo groups (figure 3). Although both treatment groups seem to have improvements in 6MWT distances over 12 months, there was not a statistically significant difference between the two treatment groups at month 12 (p=0·9303 using last observation carried forward; figure 4A). Although both treatment groups saw an improvement in NYHA functional class, there was not a statistically significant difference between the two treatment groups at month 12 (p=0·8689 using last observation carried forward (figure 4B).

The safety analysis of ixmyelocel-T was done for all 114 injected patients. There were significantly more

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safety issues in the placebo group versus ixmyelocel-T in terms of participants with related adverse events (23 [42%] of 55 *vs* 12 [20%] of 59; p=0·0154), participants with adverse events related to catheterisation or injection procedure (22 [40%] of 55 *vs* 12 [20%] of 59; p=0·0255), and overall participants with serious adverse events (41 [75%] of 55 *vs* 31 [53%] of 59; 0·0197; table 4).

Discussion

To the best of our knowledge, ixCELL-DCM is the largest randomised, placebo-controlled, double-blind multicentere study published so far of cell therapy in patients with advanced congestive heart failure due to ischaemic dilated cardiomyopathy. The study showed that bone marrow cells could be harvested, processed, expanded, and returned for transendocardial injection safely. Additionally, compared with placebo, the patients who received ixmyelocel-T showed a clinically meaningful and significant benefit in the primary endpoint, which was a composite of hard clinical events. The primary endpoint was driven by the reduction in overall all-cause deaths and cardiovascular admissions to hospital in patients who received ixmyelocel-T compared with those who received placebo. The primary endpoint (all-cause deaths and the number of cardiovascular admissions to hospital) was selected based on 2010 FDA Guidance for Industry regarding Cellular Therapy for Cardiac Disease, and is considered an appropriate endpoint for phase 3 studies.[27] Secondary endpoints dealing with LVEF, LV volumes, NYHA functional class, and 6MWT were not statistically significant. Overall, there were significantly more serious adverse events in the placebo group both related and unrelated to the injection procedure. Because ixCELL-DCM was a blinded study, the significantly higher number of safety issues in the placebo group might be associated with the injection of placebo solution into the heart. This could have an impact in future trials to ensure better safety of the placebo group in the study and a sham procedure might be required. The injection of ixmyelocel-T into the heart might confer an immunomodulatory effect as seen with other products containing MSCs, thus reducing adverse events.[14–16] Together, these data support the safety and efficacy of ixmyelocel-T in the treatment of coronary heart failure due to ischaemic dilated cardiomyopathy. The reduction in the number of cardiovascular events in patients given ixmyelocel-T in the earlier studies was comparable to the reduction observed in this study.[17] Although the improvements in 6MWT and NYHA class noted in this study are comparable to the results seen in the previous studies, the patients given placebo had improvements as well.[17] The control group in the previous unblinded studies was standard of care.

Clinical trials using only autologous BMMNCs have shown modest improvement in functional parameters, but have not had a significant effect on clinical outcomes of the treated patients.[7–13] The National Institutes of Health-sponsored cardiovascular cell therapy network (CCTRN) FOCUS trial, which enrolled 92 patients, showed a significant (2·7%) improvement in LVEF, but no improvement in maximal oxygen consumption or in LVESV in patients with ischaemic cardiomyopathy who underwent intramyocardial delivery of 100 million autologous BMMNC.[13] The study also failed to show an improvement in clinical outcomes in the treated patients. However, this might be due to the fact that age and medical comorbidities from heart failure decreased the number, quality, and potency of autologous BMMNC.[21]

Several novel approaches have been used to treat heart failure including specific cell populations such as autologous MSCs,[22] the use of allogeneic cells,[23] the use of cardiac derived cells,[24,25] or expanded or enhanced autologous bone marrow-derived cells.[26] All of these have had promising early results, but ixCELL-DCM is the first study, to our knowledge, to show meaningful clinical cardiac driven events showing a benefit in favour of cell therapy.

This study has several limitations. The sample size was only powered for the prespecified primary endpoint in the per protocol population. It was not powered for time to first cardiac event, win ratio, or any of the secondary

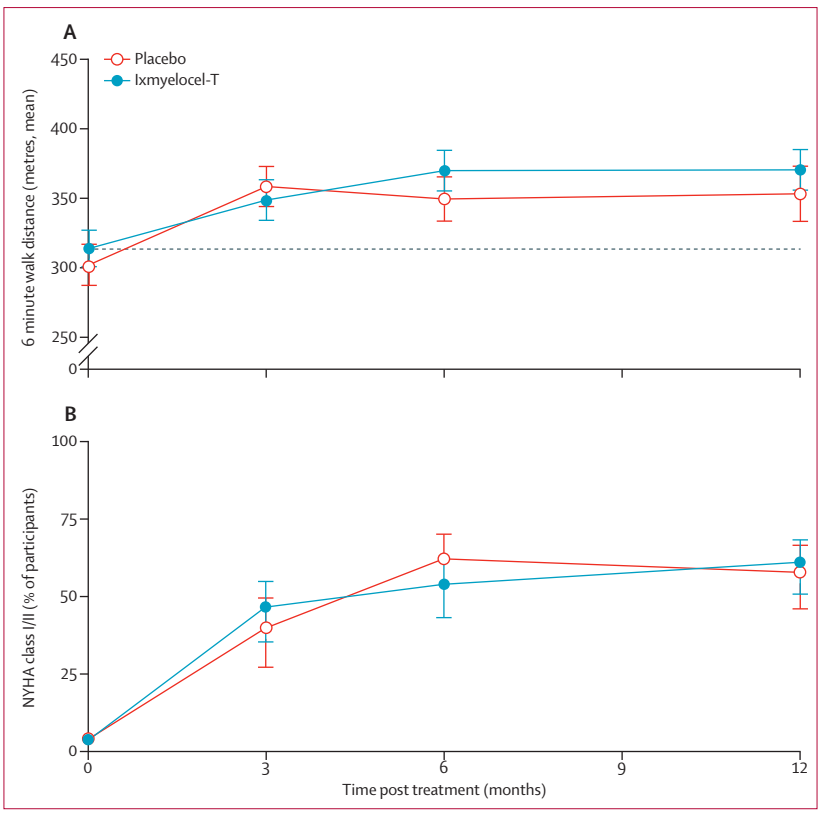

Figure 4: **6-min walk test and NHYA class functional changes**
Data are mean, error bars show SEM. 6-min walk time with ixmyelocel-T did not differ significantly when compared with control (A). New York Heart Association functional status did not show a significant difference when compared with the control group (B). For the 6-min walk test, 50, 43, 42, and 36 patients in the placebo group provided data at baseline, months 3, 6, and 12, respectively. 57, 54, 52, and 46 patients in the ixmyelocel-T group provided data at baseline, months 3, 6, 12, respectively. For the NHYA classification, 51, 48, 42, and 40 patients in the placebo group had assessments at baseline, months 3, 6, and 12, respectively. 57, 56, 54, and 51 patients in the ixmyelocel-T group provided data at baseline, months 3, 6, and 12, respectively.

	Placebo (n=55)	Ixmyelocel-T (n=59)	p value
Participants with adverse events	51 (93%)	52 (88%)	0·75
Participants with major adverse cardiovascular events	23 (42%)	16 (27%)	0·12
Participants with related adverse events	23 (42%)	12 (20%)	0·0015
Participants with adverse events related to catheter injection procedure	22 (40%)	12 (20%)	0·0255
Participants with adverse events related to investigational product	7 (13%)	4 (7%)	0·35
Participants with serious adverse events	41 (75%)	31 (53%)	0·0197
Participants with related serious adverse events	10 (18%)	6 (10%)	0·28
Participants with serious adverse events related to catheter injection procedure	9 (16%)	6 (10%)	0·41
Participants with serious adverse events related to investigational product	4 (7%)	2 (3%)	0·43
Participant deaths due to adverse events	8 (15%)	4 (7%)	0·23
Total number of adverse events	344	323	..
Total number of major adverse cardiovascular events	38 (11%)	31 (10%)	..
Total number of related adverse events	42 (12%)	27 (8%)	..
Total number of adverse events related to catheter injection procedure	37 (11%)	25 (8%)	..
Total number of adverse events related to investigational product	18 (5%)	13 (4%)	..
Total number of serious adverse events	124 (36%)	73 (23%)	..
Total number of related serious adverse events	12 (3%)	14 (4%)	..
Total number of serious adverse events related to catheter injection procedure	10 (3%)	13 (4%)	..
Total number of serious adverse events related to investigational product	6 (2%)	8 (2%)	..

Table 4: **Safety assessment of ixmyelocel-T**

endpoints in an intent-to-treat population. The imaging was based at an independent core laboratory, but it was echocardiography, not higher resolution MRI, which might affect both function and volumes. However, because most patients with end-stage coronary heart failure have an AICD place, this also restricts optimal high resolution imaging. Because this study was modest in size and designed to determine if ixmyelocel-T could reduce the number of events by about 50%, the primary efficacy analysis was done in the treated per-protocol population. A modified ITT analysis has been included in the appendix (pp 1–2) and the results are consistent with the per-protocol analysis.

In conclusion, the transendocardial delivery of ixmyelocel-T resulted in a significant reduction in clinical cardiac events driven by both cardiac mortality and cardiac admissions to hospital at 12 months compared with placebo. Ixmyelocel-T could be a cell therapy option for patients with NYHA class III/IV ischaemic congestive heart failure who have exhausted optimised medical therapy. To the best of our knowledge, ixCELL-DCM is the largest randomised double-blind clinical trial to date for cell therapy use in congestive heart failure. The effect of an autologous biological agent on the clinical outcomes of ischaemic dilated cardiomyopathy has great potential for the future of congestive heart failure management.

Contributors

All authors contributed to the interpretation of results, writing of the review, and approved the decision to submit the review for publication. ANP, TDH, AAQ, GLS, RDA, CT, CE, ASD, and AD were investigators in this study. ANP, TDH, AER, JG, and DR were involved in study design. ANP wrote and prepared the first draft of the review, with input from the other authors.

Declaration of interests

ANP, TDH, GLS, ASD, and AD received financial support from the Vericel Corporation in the form of grants and personal fees. AER, JG, and DR were employees of the Vericel Corporation during the ixCELL-DCM trial. AAQ, RDA, CT, and CE declare no competing interests.

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