Randomised trial of combination cytokine and adult autologous bone marrow progenitor cell administration in patients with non-ischaemic dilated cardiomyopathy

Final Report for the REGENERATE-DCM

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Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DCM	Idiopathic Dilated Cardiomyopathy
DMC	Data Monitoring Committee
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISRCTN	International Standard Randomised
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedures
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SSAR	Suspected Serious Adverse Reaction
Subject	An individual who takes part in a clinical trial
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

1 Overview:

1.1 Background:

Small numbers of open-labelled and pilot studies have separately assessed the benefit of bone marrow derived cells (BMC) or cytokine therapy in dilated cardiomyopathy (DCM) with mixed results. We present the REGENERATE-DCM trial, the first randomised, placebo-controlled trial of BMC combined with adjunctive granulocyte colony stimulating factor (G-CSF) administration in patients with DCM.

1.2 Methods:

A phase II randomized, placebo-controlled trial of DCM patients with significant cardiac dysfunction were enrolled into four groups to determine whether G-CSF administration with or without intracoronary delivery of BMC improves global left ventricular (LV) function (ClinicalTrials.gov: NCT01302171 and EudraCT:2009-013112-12). 60 Patients with DCM with a documented LV ejection fraction (LVEF) at referral of ≤45%, NYHA ≥ 2 and no secondary cause for the cardiomyopathy were randomized equally into four groups: peripheral placebo (saline), peripheral G-CSF, peripheral G-CSF & intracoronary serum and peripheral G-CSF and intracoronary BMC. All patients received 5-days of G-CSF (apart from peripheral placebo arm), followed by bone marrow harvest and processing on day six in the intracoronary group with intracoronary infusion on the same day.

1.3 Findings:

At three months, peripheral G-CSF and intracoronary BMC therapy was associated with a 5·37% increase in LVEF (38·30 ±12·97 from 32·93 ± 16·46 p=0·014), which was maintained to one year. This was associated with a decrease in NYHA classification at three months and one year, reduced NT-pro BNP, improved exercise capacity at one year and improved quality of life at three months and one year. No significant change in LVEF was seen in the remaining groups.

1.4 Interpretation:

This is the first randomized placebo-controlled trial with a novel combination of G-CSF and intracoronary cell therapy that demonstrates an improvement in cardiac function, symptoms and biochemical parameters in patients with DCM.

1.5 Funding:

The Heart Cell Foundation, Barts and the London Charity and Chugai Pharmaceutical. Sponsorship from Queen Mary Unisertiy of London.

1.6 Administrative Structure:

Please see Appendix 1

1.7 Steering Committee:

Please see Appendix 1

2 Introduction

Non-ischeamic dilated cardiomyopathy (DCM) is a leading cause of heart failure and the most common indication for transplantation worldwide(1, 2). The prevalence of DCM is estimated at 1 in 2500 and although a proportion of patients recover cardiac function, the majority suffer a progressive decline in left ventricular ejection fraction (LVEF)(3) with high levels of morbidity and mortality despite optimal medical care(4).

Novel approaches to promote recovery of myocardial function in DCM have included cytokine and cell therapies. Clinical investigation of cytokine therapy alone has been limited and has failed to deliver long-lasting improvements in cardiac function(5). Autologous bone marrow derived cell (BMC) therapy has moved rapidly from proof of concept in preclinical experiments to clinical trials of cardiac repair. These trials have been designed in the most part to assess the therapeutic potential of autologous cell therapy for patients with acute myocardial infarction or heart failure secondary to ischaemic heart disease. Although these early Phase I/II clinical trials have demonstrated mixed results, meta-analysis has suggested that autologous cell therapy has therapeutic potential in these patient groups(6). However improvements in the intermediate outcome measures used in these trials has been modest, suggesting that adjunctive or alternative types of cell therapy may be needed to achieve clinically meaningful results.

Patients with DCM are a small proportion of those entered into these early stage trials. A recent meta-analysis and review suggested that autologous cell therapy has beneficial effects on intermediate outcomes of disease such as cardiac function in patients with DCM(7). Here we report the results of the first, randomized, blinded (within arm), placebo controlled trial combining autologous cell therapy with adjunctive cytokine - granulocyte colony stimulating factor (G-CSF) - in the treatment of patients with DCM. We hypothesized that intracoronary autologous BMC administration would augment the pleotropic effects of G-CSF on cardiac function leading to an increase in LVEF accompanied by improvement in symptoms and biochemical markers of heart failure.

3 Methods

3.1 Trial

The study is a randomised blinded (within arm), single centre, placebo-controlled Phase II trial to determine whether the administration of G-CSF alone to patients with DCM will lead to an improvement in LVEF and whether adjunctive autologous BMC administration leads to an additional sustained benefit on cardiac function. The trial was approved by an independent ethics committee, the Medicines and Healthcare Products Regulatory Agency (MHRA), registered at approved registries (NCT01302171, EudraCT nr. 2009-013112-12) and was performed in accordance with the Declaration of Helsinki (1993) and the principles of the International Conference of Harmonization– Good Clinical Practice (ICH-GCP) guidelines, any protocol amendments were submitted and approved by the local R+D, ethics and MHRA.

3.2 Population

Potential patients were assessed after referral from heart failure specialists at the London Chest Hospital, the Heart Hospital London and the Royal Brompton Hospital London. Inclusion criteria included a diagnosis of non-ischaemic DCM, a LVEF of less than 45% (assessed by echocardiography at referral), symptoms classed as NYHA 2 or greater and on optimal medical treatment (established for at least six months).

3.3 Randomisation and treatment

Medical professionals who were singed to the delegation log performed full informed consent for the trial, all patients who underwent consenting received a patients information sheet (PIS) to read fully prior to consenting. After which patients were randomised using a dedicated trial software system (IHD Clinical Bishops Stortford, Herts, UK) (1:1 – simple randomisation algorithm) to either the 'peripheral group' where half received peripheral subcutaneous injected saline (peripheral placebo group) and half G-CSF (Granocyte™, Chugai Pharmaceutical UK Ltd, Mulliner House, London) (10 µg/kg/day) for five days (peripheral G-CSF group), or the 'intracoronary (interventional) group' where following five days of G-CSF all patients underwent bone marrow harvest with half receiving the intracoronary infusion of autologous BMC (IC BMC group) and the remainder intracoronary infusion of serum (IC serum group). Intracoronary injection was standardised to deliver cells equally between the major epicardial vessels via the stop flow method as previously described(8).

3.4 Endpoints and definitions

The primary end point was absolute change in global LVEF assessed by advanced cardiac imaging at three months compared to baseline. Secondary imaging endpoints included change in LVEF at one year (compared to baseline) and changes in LV volumes and myocardial mass from baseline to three months and one year. Secondary endpoints included change in exercise capacity (VO_2 Peak), NT-proBNP levels, and NYHA classification at three months compared to baseline and quality of life as assessed by EQ5D and Kansas City Cardiomyopathy Questionnaire (KCCQ) at three months and one year. MACE (defined as all-cause death, myocardial infarction, hospitalisation for heart failure, or major arrhythmias - defined as VT/VF) were assessed at three months and one year. The safety of the intracoronary infusion was assessed with venous blood samples taken at 12 hours post infusion, measuring for creatine kinase (CK) and Troponin T concentrations as well as documentation of procedural complications.

3.5 Advanced cardiac imaging

Cardiovascular Magnetic Resonance (CMR) or cardiac computed tomography (CT) for those unable to undergo CMR (e.g. cardiac devices, claustrophobia etc) were performed at baseline and three months. Conformity of the imaging modality was assessed separately to ensure reproducibility and sensitivity. The standard error of measurement of MRI and CT was 1.93% and 2.3% respectively. Multi-phase cardiac data sets with full left ventricular coverage were acquired using standard protocols(9, 10). The scans were anonymised, batched and analysed (Circulation, Siemens for CT and CMRtools, Cardiovascular Imaging Solutions, London, UK) in blinded fashion by two experienced operators (for full details of CT and CMR imaging protocols see online supplementary information). (See Appendix 2)

3.6 Pulmonary Exercise testing

Patients underwent exercise testing using a modified Bruce treadmill test performed by an independent team at Royal Brompton NHS Trust. Patients were monitored throughout with tests being terminated by physiological markers (ST changes, arrhythmias or chest pain) or by patient request.

3.7 Statistical Design and Analysis

The study was powered to the primary end point of change in LVEF at three months as measured by advanced cardiac imaging. The sample size was calculated to detect an improvement in LVEF of 3·5% with a power of 90% and significance level of 5%, as demonstrated by a contemporary meta-analysis of previous cell therapy Phase I/II trials(11). The standard error for the advanced imaging LV measurements was estimated as 4%.

Analysis was based on the intention-to-treat principle. Baseline demographic and clinical variables were summarised for each group of the study. Continuous variables are presented as means ± SD and categorical variables are presented as percentages. 95% confidence intervals (CI) are given. P values are two-sided with a value of < 0·05 considered to indicate statistical significance. Within group comparisons were performed using the paired T test. Between group comparisons were performed using analysis of variance (ANOVA) followed by the Bonferroni multiple-comparison *post hoc* test. All statistical analyses were performed using SPSS version 19 (IBM Corp. Armonk, NY, USA) and graphs produced using Graphpad Prism version 5.0 (GraphPad Software, San Diego, CA).

3.8 Funding

The trial was supported by unrestricted grants from the Heart Cells Foundation and Barts and the London Charity. Chugai Pharmaceutical donated supplies of G-CSF and pharmaceutical costs.

4 Results

Between July 6th 2010 to 24th April 2012, 258 patients were screened after referral from specialised heart failure clinics across the UK to the London Chest Hospital. Of these patients, 132 were excluded for the following reasons: patients baseline NYHA classification<2 (n=30), LVEF<10% or >45% (n=46) on referral centre echocardiogram, secondary cause of DCM (n=15), paroxysmal or permanent atrial fibrillation without permanent pacing (n=14), weight >140kg (n=1), creatinine >200µmol/l (n=3), and other (including age <18, and malignancy and diagnosis of DCM not clear; n=16). This left 126 suitable patients, of which 66 declined participation. Data are presented for the 60 patients who were randomised to the peripheral group [peripheral G-CSF (n=15), peripheral placebo (n=15)] and the intracoronary group [intracoronary infusion of BMC (n=15), intracoronary infusion of serum (n=15)] (Figure 1). A total of 58 patients reached the 3-month primary end point and 53 patients reached one year follow up.

The mean age for the total population was 54·55 ± 11·19 years, and 70% were male. At baseline, the four groups were similar with regard to age, sex, LVEF, plasma NT-proBNP concentration, or medical/ device management. (Table 1)

In the cell treated group the mean number of BMC injected was $216{\cdot}01 \times 10^6$ ± 221·77. Of this, the mean number of CD34+ cells injected (as a measure of stem like cell potential of the BMC population) was $4{\cdot}90 \times 10^6$ ± 2·75. In 10 patients, progenitor cells were injected into all three coronary arteries and in five patients progenitor cells were injected into the left anterior descending and circumflex arteries alone. No cases of distal coronary artery occlusion, acute cardiac dysfunction, or significant CK release occurred. One patient suffered a localised coronary dissection during the infusion and was treated with coronary stenting but with no significant change in CK. No patients experienced an arrhythmia (Ventricular Tachycardia or Ventricular Fibrillation) during the intracoronary infusion. Average plasma troponin T levels were 0·09 ± 0·01 ng/mL at baseline, 0·11 ± 0·02 ng/mL six hours after the procedure, and 0·08 ± 0·01 ng/mL 12 hours after the procedure. At three months there was no evidence of a difference in the troponin level between the intracoronary groups. Peripheral concentrations of CD34+ cells was significantly greater in patients who had G-CSF therapy. The average plasma CD34+ concentration increased from 3·94 ± 3·54/uL at baseline to 56·47 ± 45·13/uL after five

days of G-CSF therapy; p=<0·0001. Patients who received placebo peripheral injections showed almost no increase in circulating CD34+ counts (4·64 ± 3·19/ul at baseline to 5·00 ± 3·04/ul; p=0·5791).

4.1 Left Ventricular Ejection Fraction

Twenty-two patients underwent CMR assessment of cardiac function whilst the remaining 38 underwent CT scanning (Table S1). Baseline measurements of LVEF did not differ significantly between the treatment groups (Table S1). Global LVEF increased significantly in the IC BMC group by a mean of 5·37% from 32·93 ± 16·46% at baseline to 38·30 ± 12·97% at three months (p=0·014, n=15) (Figure 2i). This increase in LVEF in the IC cell treated group was significantly higher when compared to the IC placebo (6·47%; 95% CI, 1·09 to 11·84; p=0·0193) and peripheral placebo groups (6·44%; 95% CI, 0·97 to 11·91; p=0·0219). No significant change was seen in any of the other treatment groups between baseline and three months (peripheral G-CSF group mean difference: 0·14%; 95% CI, -4·504 to 4·790; p=0·9481, n=14; peripheral placebo group mean diff-1·07%; 95% CI, -5·755 to 3·612; p=0·6294, n=14; serum group mean diff: -1·1; 95% CI, -4·230 to 2·030; p=0·4634, n=15).

At one year the improvement in cardiac function was maintained in the IC BMC group with a 7·04% increase in LVEF from baseline (42·92 ± 12·20% from 35·88 ± 15·45%;p=0·0067, n=13). Post hoc analysis using one way ANOVA with bonferroni correction demonstrated a significant increase in LVEF comparing the IC BMC group to controls (6·31% difference in IC BMC group treated vs IC placebo; 95% CI, -12·37 to -0·2464; p=0·0420, n=13 and 8·96% difference in IC BMC group treated vs peripheral placebo group; 95% CI, -16·31 to -1·609; p=0·0141, n=13). In the patients who showed improvement in LVEF at one year the number of cells injected was positively associated with the improvement in LVEF (r^2=0·4848, p=0·037, supplementary figure S1)

4.2 Plasma NT-proBNP concentration

Blood analysis was performed on samples at baseline, three months and one year for each patient; statistical analysis was performed after logarithmic transformation of all NT-proBNP values due to a non-normal distribution. There was significant decrease in NT-proBNP in the IC BMC group at one year (993·0 ± 1023 pg/ml to 857·9 ± 1291 pg/ml; p=0·0023). This decrease was significantly different from the change seen in the

comparable IC serum group (diff: 316·0 pg/ml: 95% CI, -213·3 to 845·3; p=0·0420). Both peripheral groups showed non-significant small improvements in NT-proBNP at one year (Figure 2iii and Table S3)

4.3 Exercise capacity and VO_2 Peak

Fifty-six patients underwent pulmonary exercise testing at both baseline and three months with 49 undergoing further assessment at one year. At three months the IC BMC group showed the greatest improvement in VO_2 peak (17·67 ± 5·76 mls/kg/minto 19·13 ± 7·51 mls/kg/min) although this was not statistically significant (p=0·16877). At one year there was a significant improvement in VO_2 peak (18·03 ± 5·86 mls/kg/min to 21·23 ± 6·23 mls/kg/min; p=0·0179) (Figure 2ii). The difference in exercise capacity from baseline to one year was significantly greater when compared to the change in the peripheral placebo group (p=0·0192).

Further analysis using exercise time and maximum speed as endpoints of exercise capacity showed a significant improvement in maximum speed reached at both three months (1·95 ± 0·71 mph to 2·55 ± 1·06 mph; p=0·0192) and one year (1·99 ± 0·75 mph to 3·27 ± 1·06 mph; p=0·0164) in the IC BMC group with an associated increase in exercise time at both three months (424·1 ± 183·2 seconds to 504·0 ± 239·0 seconds; p=0·0146) and one year 415·8 ± 183·7 seconds to 578·1 ± 272·8 seconds, p=0·0131). No other group showed any significant changes (Table S2).

4.4 Left Ventricular Dimensions

There was no evidence of difference between one year and baseline values were seen in any other treatment group. No evidence of a difference was seen in LV end systolic volume (LVESV), LV end diastolic volume (LVEDV), stroke volume (SV) or myocardial mass (MM) over time in any of the treatment groups (Table S1).

4.5 NYHA

NYHA classification improved in the IC BMC group with 6 (40%) patients improving by 1 NYHA class and no patients having a deterioration in their classification at three months. This compared to the IC serum group where only 1 (6·7%) patient showed an improvement, the peripheral G-CSF group, where 3 (20%) patients showed improvement and in the peripheral placebo group where no patients showed an improvement. The

percentage of patients who showed improvement in their NYHA classification was significantly higher in the IC BMC group (χ^2=14·92, dif=6; p=0·02). At one year this pattern continued with 8 (66·7%) patients improving in the intracoronary BMC group, 3 (23·0%) patients improving in the intracoronary serum group, 3 (21·4%) patients improving in the peripheral G-CSF group and only 1 (8·3%) patients improving in the peripheral placebo group (χ^2=12·61, dif=6; p=0·0497) (Figure 3).

4.6 Quality of Life

Using the EQ5D questionnaire all groups showed no evidence of a difference in quality of life parameters at three months. At one year the EQ5D showed evidence of improvement in quality of life in the peripheral G-CSF group (0·462 ± 0·350 to 0·647 ± 0·236; p=0·013) however this was not reflected in the paired visual score (62·33 ± 16·81 to 69·56 ± 13·53; p=0·400).

Using the KCCQ there was evidence of improvements in the patient's symptoms and social factors (clinical summary score) in the IC BMC group at both three months (54·64 ± 21·80 to 64·34 ± 25·83; p=0·0028) and maintained at one year (63·67 ± 27·62; p=0·0005 compared to baseline). In 'overview, KCCQ summary' of all therapy groups showed improvement in scores at one year with significant improvements in both the IC BMC group (38·66 ± 20·96 to 56·27 ± 29·96; (p=0·0053) and peripheral G-CSF group (50·81 ± 21·27 to 60·26 ± 21·16; (p=0·0438)(Table S4).

4.7 Safety

There were no complications or adverse events associated with G-CSF therapy, although a small number of patients reported a recognised common side effect of long bone pain during therapy. There was one report of MACE in each of the peripheral groups at one year, two reports of MACE in the IC BMC group and three reports of MACE in the IC serum group at one year (Table S5).

5 Discussion

This is the first randomised trial of patients with DCM assessing the combination of cell and cytokine therapy to demonstrate a significant increase in cardiac function supported by improvements in symptoms, exercise physiology and biochemical markers of heart failure. Although for pragmatic and ethical reasons the amount of bone marrow harvested was standardised (rather than the number of cells injected) it is interesting to note that a dose response relationship was seen between total number of cells injected and change in LVEF in the IC BMC group supporting a causal relationship. G-CSF alone did not seem to have a beneficial effect on cardiac function. Compared to the interventional control group, the G-CSF/IC BMC patients demonstrated a 5·37% increase in LVEF at three months, which was maintained at one year. This LVEF improvement was associated with significant improvements in the clinical parameters of NYHA class, exercise capacity and quality of life as well as a decline in the biochemical marker NT-pro BNP at one year. The remaining groups treated with G-CSF (intracoronary serum and G-CSF alone) failed to show evidence of improvement in any of these end-points at either three months or one year. These results therefore demonstrate the beneficial effects across multiple clinical and intermediate parameters of combined cell and cytokine therapy in a randomized control trial of patients diagnosed with DCM. Since the trial was designed to test whether BMC in addition to G-CSF provided added benefits it is not clear whether cell therapy alone would have had a similar effect.

Similar beneficial effects on cardiac function with BMC therapy have been shown in other early phase studies(12, 13), with the most recent demonstrating improvements out to five years post therapy(14). However no study has been performed with a randomised interventional control group blinded to the investigators. Previous studies have also used G-CSF alone but few have controlled for the possibility that this cytokine may have a direct effect on cardiac function as has been previously suggested(15, 16). Early preclinical and initial Phase I trials suggested that G-CSF administration was safe in the treatment of DCM and possibly associated with improvements in LVEF(17). REGENERATE DCM is the first trial designed with a separate interventional and cytokine only control group. It should be noted that although the peripheral G-CSF group did not show an improvement in intermediate and clinical end-points there was an improvement in quality of life scores highlighting the need for rigorous study design involving appropriate control arms as previously suggested(7).

The study population enrolled in REGENERATE DCM was typical of a DCM population with similar baseline characteristics and medical therapy to patients in other published trials(18, 19). The biochemical markers indicating severity of heart failure were similar across all groups with a plasma NT-proBNP concentration greater than 1000 pg/ml suggestive of significant left ventricular dysfunction. The patient population had high levels of optimal medical therapy in all groups and were stabilised prior to randomisation. The improvement in cardiac function and symptoms in the cell treated group was thus unlikely to be due to differences in medical therapy between the groups(20). The patient population also had appropriate levels of 'device therapy' in keeping with current international guidelines, and was consistent across groups(21).

Although the results of the REGENERATE DCM trial suggest a beneficial effect of combination G-CSF and BMC therapy this is a Phase II trial powered around intermediate efficacy measures. The trial met its statistical end-point criteria despite the small sample size. The primary end-point was supported by relevant changes in the secondary end-points which adds reassurance to the findings despite the study size. The study could not be completely blinded across all arms due to the invasive nature of the intracoronary arm. Nonetheless the investigators and patients were blinded within arm between active treatment and placebo. All analyses were undertaken by clinicians using anonymised data who were therefore blinded to the treatment groups. Advanced cardiac imaging was used to measure the primary end-point but patients underwent either paired MRI or CT analysis depending upon whether they were excluded from the MRI scanner due to metallic implants or previous claustrophobia. Since the scans were paired and the primary end-point was based on within group measures any modality related differences in the measurements of cardiac function would not account for the significant findings. Furthermore the standard error of measurement of MRI and CT was similar.

The results of REGENERATE DCM therefore demonstrate improvement in a panel of measures of cardiac function accompanied by improvement in symptoms. In particular the change in plasma NT-proBNP at one year suggest that cell therapy may lead to a long-term outcome benefit in these patients(22) and therefore warrants further investigation using the methodology described in this manuscript in a Phase III trial.

6 Conclusion

The intracoronary infusion of autologous unfractionated BMC in combination with G-CSF therapy in patients with DCM appears to be safe and is associated with an improvement in LVEF three months after therapy, which is maintained at one year. These functional differences were accompanied by improvement in a panel of biochemical and symptom related outcomes supporting a potential clinical benefit of this therapy.

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Panel: Research in Context

Systematic review

The PubMed database was searched for original papers of phase II clinical trials using the term “stem cells”, “G-CSF”, “bone marrow’, “dilated cardiomyopathy”, “cytokine” and “stem cell therapy” and no results were found. An additional search was performed with the same parameters looking at all clinical trials and a single non-randomised trial looking at the effects of G-CSF between DCM and Ischemic cardiomyopathy patients with no intracoronary intervention performed was found(23). A recent systematic review concluded that cell therapy is novel remedy for dilated cardiomyopathy however there is a need for adequate placebo controlled trials to validate safety and efficacy(7). REGENERATE DCM represents one of the first approaches to address this question.

Interpretation

REGENERATE DCM is the first randomised trial to test the combination of cytokine and intra-coronary bone marrow cell therapy in patients with dilated cardiomyopathy who remain symptomatic despite optimal conventional care. The trial design addresses previously unanswered questions from the early phase I and open-labelled trials regarding safety and efficacy(13, 14). The results of REGENERATE DCM are important since they suggest that combination cytokine and autologous cell therapy may have important therapeutic advantages beyond the conventional management of patients with dilated cardiomyopathy. Currently there are no new treatments for patients with DCM and heart transplantation – the only definitive destination therapy – is only available for very small proportion of patients with this condition. The methods used in REGENERATE DCM therefore warrant further investigation in an outcome study to address this unmet need.

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Table 1. Baseline characteristics of the study population

	Peripheral Placebo (n = 14)	Peripheral G-CSF (n=14)	Between Group p-value	Intracoronary Serum (n = 15)	Intracoronary BMC (n = 15)	Between Group p-value
Age (years), mean (SD)	56·79 (9·84)	54·57 (9·76)	-	54·87 (10·86)	51·67 (12·32)	-
Sex (M/F), (No./No.)	12/2	10/4	-	9/6	10/5	-
BMI (kg/m²), mean (SD)	29·15 (4·48)	29·19 (5·19)	-	28·26 (9·10)	27·23 (4·33)	-
Hypertension, No. (%)	2 (14·2%)	1 (7·1%)		1 (6·6%)	2 (13·3%)	
Hypercholesterolemia, No. (%)	3 (21·4%)	2 (14·2%)		1 (6·6%)	0 (0%)	
Diabetes mellitus, No. (%)	2 (14·2%)	1 (7·1%)		1 (6·6%)	2 (13·3%)	
Active smoker, No. (%)	2 (14·2%)	1 (7·1%)		2 (13·3%)	2 (13·3%)	
Family history of any heart disease, No. (%)	2 (14·2%)	1 (7·1%)		2 (13·3%)	2 (13·3%)	
Time from diagnosis to randomisation (y), mean (SD)	5·43 ± 0·98	7·6 ± 2·09		8·00 ± 1·61	4·9 ± 0·96	
			-			-
Medical therapy			-			-
ACEi, No. (%)	8 (57·1%)	5 (35·7%)	-	11 (73·3%)	9 (59·9%)	-
ARB, No. (%)	5 (35·7%)	9 (64·2%)		5 (33·3%)	5 (33·3%)	
ACEi/ARB, No. (%)	13 (92·9%)	14 (100%)	-	15 (100%)	15 (100%)	-
B-Blockers, No. (%)	14 (100%)	12(83·7%)	-	13 (86·6%)	13 (86·6%)	-
Diuretics, No. (%)	8 (57·1%)	8 (57·1%)		8 (53·3%)	9 (59·9%)	
Aldosterone Antagonists, No. (%)	11 (78,6%)	7 (50·0%)		12 (79·9%)	10 (66·6%)	
Digoxin, No. (%)	2(14·2%)	5 (35·7%)	-	4 (26·6%)	6 (39·9%)	-
			-			-
LVEF			-			-
Baseline; mean (SD)	29·75 (9·191)	36·5 (13·26)	0·0994	41·70 (15·25)	32·93 (16·46)	0·1414
			-			-
Device therapy			-			-
ICD, No. (%)	3 (21·4%)	5 (35·7%)		4 (26·6%)	4 (26·6%)	
Biventricular Pacemaker, No. (%)	1 (7·1%)	0 (0%)		2 (13·3%)	2 (13·3%)	
CRT-D, No. (%)	6 (42·9%)	4 (28·6%)	-	3 (19·9%)	7 (46·6%)	-
Total prognostic therapy, No. (%)	7 (50·0%)	4 (28·6%)	-	5 (33·3%)	9 (59·9%)	-

Plus-minus values are mean ± SD. No denotes number

BMI - body mass index, G-CSF - granulocyte-colony stimulating factor, ACE - angiotensin-converting enzyme inhibitor, ARB - Angiotensin receptor blocker, ICD - implantable cardioverter-defibrillator and CRT-D - Cardiac Resynchronization Therapy Defibrillators, LVEF – Left ventricular ejection fraction

Figure 1:

Flow chart of the study design summarizing flow of patients through the trial.

Figure 1

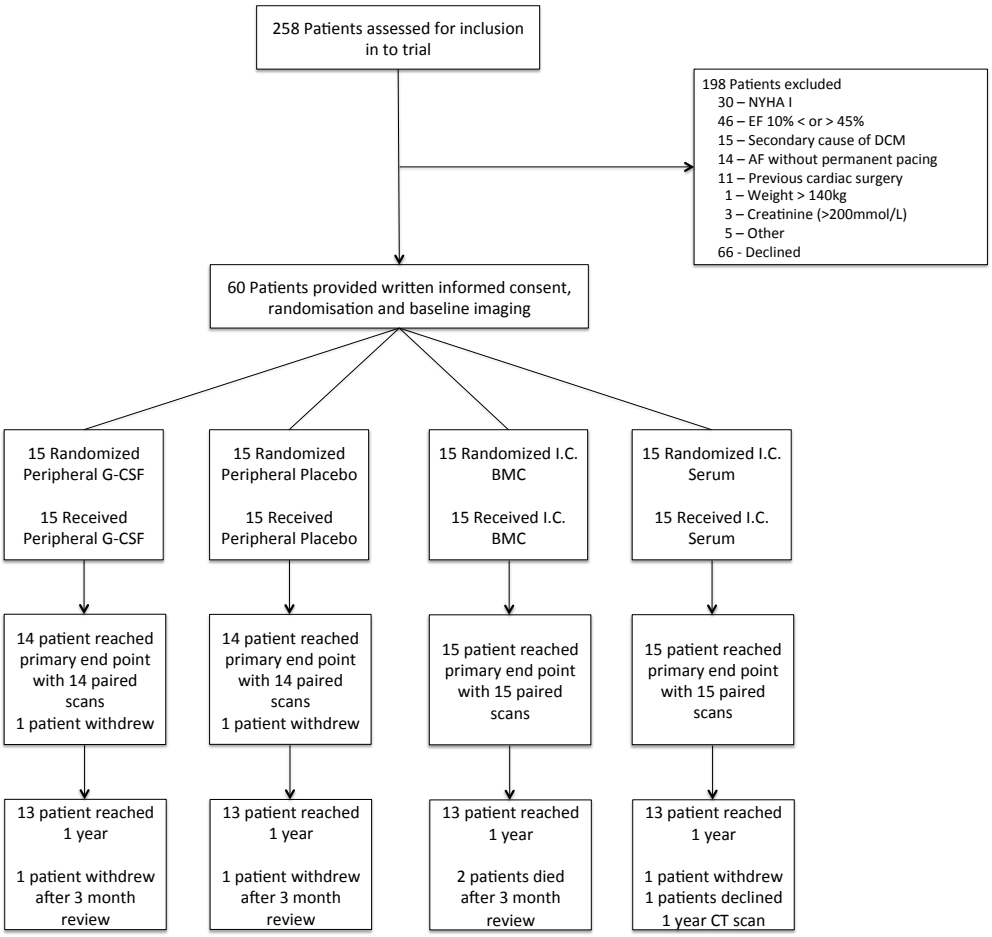

Figure 2:

Box and whisker plots (median and range) primary and secondary end points of the REGENERATE DCM trial measured at 3 months and 1 year. Patient groups (A) Peripheral G-CSF, (B) Peripheral placebo, (C) intracoronary BMC infusion, (D) intracoronary serum infusion.

End points: (i) Left ventricular ejection fraction,(ii) VO_2 Max & (iii) NT-proBNP.

* denotes significance with p<0.05 and ** denotes significance with p<0.01

Figure 2i.

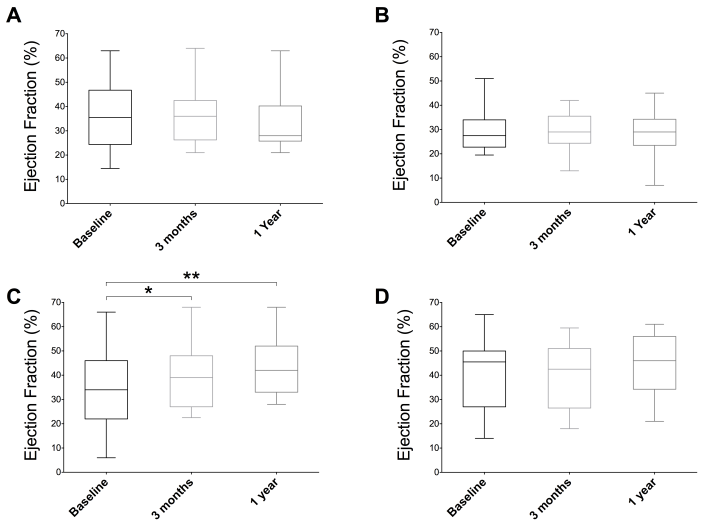

Figure 2ii

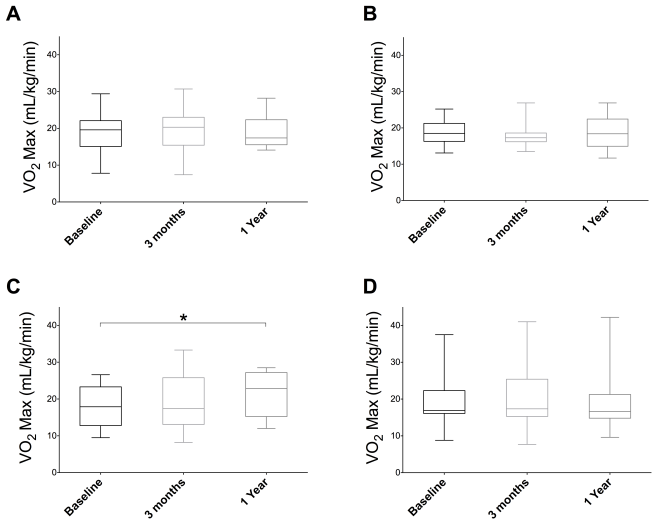

Figure 2iii

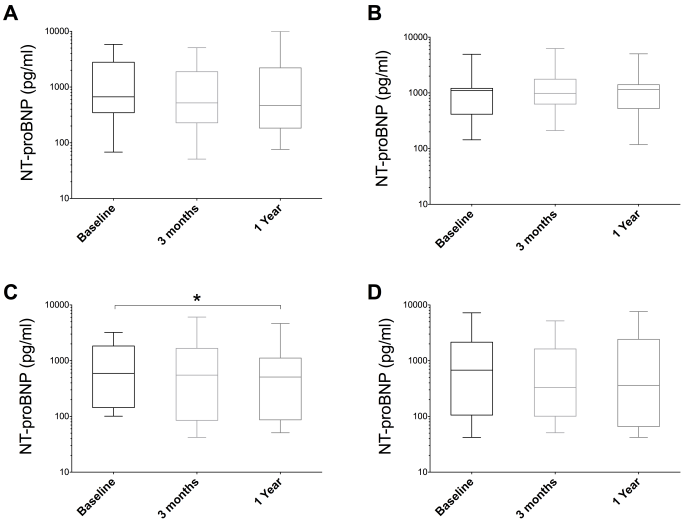

Figure 3:

Bar chart showing symptomatic change as measured by change in NYHA classification per treatment group at 3 months and 1 year. Percentages reflect number of patients that have worsened, improved or remain unchanged compared to baseline. (Note: Unchanged is not represented by area)

* denotes significance with p<0.05