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The effect of intracoronary infusion of bone marrow-derived mononuclear cells on all-cause mortality in acute myocardial infarction: rationale and design of the BAMI trial

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Over the past 13 years bone marrow-derived mononuclear cells (BM-MNCs) have been widely investigated for clinical efficacy in patients following acute myocardial infarction (AMI). These early phase II trials have used various surrogate markers to judge efficacy and, although promising, the results have been inconsistent. The phase III BAMI trial has therefore been designed to demonstrate that intracoronary infusion of BM-MNCs is safe and will significantly reduce the time to first occurrence of all-cause death in patients with reduced left ventricular ejection fraction after successful reperfusion for ST-elevation AMI (powered with the aim of detecting a 25% reduction in all-cause mortality). This is a multinational, multicentre, randomized, open-label, controlled, parallel-group phase III study aiming to enrol approximately 3000 patients in all-cause mortality. This is a multinational, multicentre, randomized, open-label, controlled, parallel-group phase III study aiming to enrol approximately 3000 patients in 11 European countries with at least 17 sites. Eligible patients who have impaired left ventricular ejection (<45%) following successful reperfusion for AMI will be randomized to treatment or control group in a 1:1 ratio. The treatment group will receive intracoronary infusion of BM-MNCs 2–8 days after successful reperfusion for AMI added on top of optimal standard of care. The control group will receive optimal standard of care. The primary endpoint is time from randomization to all-cause death. The BAMI trial is pivotal and the largest trial to date of BM-MNCs in patients with impaired left ventricular function following AMI. The aim of the trial is to provide a definitive answer as to whether BM-MNCs reduce all-cause mortality in this group of patients.

Keywords

Cell therapy • Cardiovascular disease • Bone marrow-derived mononuclear cells • Myocardial infarction • Heart failure • Cardiac regeneration • BAMI

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Introduction

Despite the widespread adoption of mechanical reperfusion for acute myocardial infarction (AMI) and the use of optimal medical therapy, the medium-to-long term mortality remains as high as 7–12%. Impaired left ventricular ejection fraction (LVEF) following AMI is a powerful predictor of mortality as well as morbidity and increased risk of hospitalization for heart failure. These realities have fuelled the search for novel therapies to improve cardiac function following AMI. Myocardial regeneration following bone marrow-derived mononuclear cell (BM-MNC) therapy was initially demonstrated in a murine model of AMI at the beginning of the 21st century. Ever since, there has been an enormous effort to try and translate this exciting pre-clinical promise into clinically meaningful benefits for patients. The results of relatively small phase II clinical trials have been heterogeneous, some showing improvement in cardiac function and others no effect of cell therapy. This may be due to a number of reasons including the difference in cell isolation and preparation protocols (different number of cells and compositions), the timing of the infusion procedure, baseline ejection fraction, and study design. Importantly, all the studies have shown relative safety and feasibility of bone marrow aspiration and infusion of cells early after AMI. In fact, meta-analysis studies have demonstrated a signal towards improved clinical outcome in patients treated with BM-MNCs, including, importantly, overall mortality. The European Society of Cardiology (ESC) task force on stem cells in cardiac disease comprises some of the key European trialists (17 members from 11 EU countries) that have contributed to clinical trials in this area and are leading experts in this field. The ESC Task Force has reached the consensus view that this therapy needs standardizing and testing in a definitive outcome endpoint clinical trial. This translated into the design of the BAMI study, the methods and rationale of which are described in this paper. The aim of the BAMI pivotal outcome trial is to demonstrate that intracoronary infusion of bone marrow-derived progenitor cells is safe and will significantly reduce the time to first occurrence of all-cause death in patients with reduced LVEF after successful reperfusion for acute ST-elevation myocardial infarction (STEMI).

Methods

The full protocol can be found in Appendix S1 in the Supplementary material online.

Study objectives

The primary endpoint of the BAMI study is time from randomization to all-cause death. Secondary efficacy endpoints include major adverse cardiac events—a full list of which is given in Table S1 in the Supplementary material online.

Overview of study flow

The BAMI study is a phase III study with a randomized controlled open-label design. Approximately 3000 STEMI patients are planned to be enrolled in 11 European countries with at least 17 sites.

Study population

A total of approximately 3000 male and female patients are planned to be enrolled in the BAMI study. Enrolment will involve at least 17 sites in 11 countries. Investigational sites will keep a logbook of all patients proposed to be included.

Table S2 in the Supplementary material online provides a full list of the inclusion and exclusion criteria for enrolment in the BAMI trial.

Patient screening and randomization

Patients will be recruited based on the existing medical information from the pool of AMI patients at the clinical centres. Patients who had primary PCI performed at clinical centres that are different from the investigational sites can also be included: interested patients may be referred for screening to any of the participating study sites within 2–4 days. Informed consent and assessment of eligibility of patients with respect to inclusion and exclusion criteria will be done at the investigational site. Written informed consent must be obtained.
Rationale and design of the BAMI trial

Figure 1 Flow-chart of t2c001 drug substance production. PBS, phosphate-buffered saline.

Study duration for study patients
Each enrolled patient will remain in the study throughout the entire study duration, with a minimum follow-up of 2 years for each patient. A study patient's participation may be terminated early for reasonable cause, such as the investigator's medical decision. At any time, the patient has the right to withdraw consent without a negative impact on her/his medical treatment. However, the investigators are encouraged to ask for the patient’s permission for further follow-up telephone contacts from those whose decision for discontinuation was based on the need for further outpatient visits.

Duration of the whole study
Patients will be enrolled during a recruitment phase of approximately 3 years. Since minimum study duration for one patient is 2 years, the
Patients with acute myocardial infarction post primary PCI

Screening phase

N = 3000 eligible AMI patients
2-6 days post primary PCI
Central reading of echocardiography (EF ≤45%)
\rightarrow randomisation 1:1
= day 0

Group 1: Control, n= 1500
No intervention = day 0

Group 2: BM-MNC, n= 1500
Bone marrow aspiration= day 0-6

Intracoronary infusion of BM-MNCs
= day 0-6 (depending on transportation and cell processing schedule) 2-8 days post PCI, and follow-up day 1 post infusion

Day 30 ± 7 days: Site visit follow-up
Month 3: Telephone follow-up
Every 3 months: Telephone follow-up

Following observation of full no. of events:
End of study visit

Day 30 ± 7 days: site follow-up
Month 3: Telephone follow-up
Every 3 months: Telephone follow-up

Following observation of full no. of events:
End of study visit

Figure 2 BAMI study flowchart. AMI, acute myocardial infarction; BM-MNC, bone marrow-derived mononuclear cell; EF, ejection fraction.

The overall study duration is approximately 5 years. The Data Monitoring Committee may terminate the study earlier based on safety concerns at any time. The sponsor may also terminate the study early for reasonable cause. Competent authorities/ethics committees retain the right for premature termination of the study according to applicable regulations. At an individual study centre, the study may be terminated early if the work performed is not compliant with Good Clinical Practice.

Sample size and statistical analysis

This trial is designed as an event-driven trial. The estimated required number of events is based on the assumptions that there will be a 12% event (death) rate at 2 years in the control group, which will be reduced to 9% (25% relative reduction, 1.355 hazard ratio) in the BM-MNC group. In addition, the study will be designed as a group-sequential study with one interim analysis performed after 150 deaths have been observed. Early termination will be possible at this stage if the experimental group shows superiority in comparison to the control group at a statistical significance level of 1%. However, all patients recruited must complete a 2 year follow-up, even if the trial is stopped prematurely. Using an alpha-spending function according to Lan–DeMets, an initial total of 450 events will be required to have 90% statistical power to detect the above treatment effect.

With an accrual period of 3 years, total study duration of 5 years and an expected drop-out rate of 10% at 2 years, it is estimated that a total of 3000 patients will be needed to observe the required number of events during the study period.

The efficacy analyses of this study will be performed on the full analysis set (FAS), including all randomized patients according to their randomized treatment. In case of many protocol violations, a per protocol set (PPS) will be defined excluding patients with serious protocol violations. Finally, a safety set will be defined, including all patients who were treated according to their actual treatment, for the assessment of safety parameters. The primary endpoint of all-cause mortality will be presented using Kaplan–Meier curves by treatment group. The curves will be compared using a log-rank test. Statistical significance will be claimed when the resulting P-value is lower than 0.043. The secondary and safety endpoints will be summarized using cumulative incidence functions (CIFs), allowing for the competing risk
A.H.-N. is an employee of t2cure, the company that has the rights to disclose. All other authors have nothing to disclose.

**Discussion**

The design of the pivotal BAMI study described above has several important considerations. This is the first phase III study of BM-MNCs in AMI, which is powered with the aim of detecting a 25% reduction in all-cause mortality. Previous trials have mainly relied on surrogate markers such as LVEF to judge efficacy. The results of these trials, listed in Table S3 in the Supplementary material online, have been inconsistent with variable or no improvement in left ventricular function. Interestingly, improved clinical outcomes including mortality and rehospitalization for heart failure have been seen in long-term follow-up of the REPAIR-AMI study. Furthermore, meta-analysis studies have also demonstrated a signal towards reduced mortality and morbidity following BM-MNC therapy. It is also important to remember that dramatic changes in LVEF were not seen in clinical trials of therapies in patients with AMI that have subsequently been shown to have significant reductions in mortality. The purpose of the BAMI trial is therefore to investigate this potential mortality-lowering effect of BM-MNC therapy in an appropriately powered study.

A randomized design with a control group not undergoing any planned interventional procedure (i.e. bone marrow aspiration or PCI) was chosen to enable evaluation of the addition of the study treatment on top of the current best standard of care for three reasons. First, inclusion of a true placebo group (sham-intervention) is generally ethically controversial. Second, the previous double-blind, placebo-controlled, REPAIR-AMI trial has already documented a beneficial effect of intracoronary administration of bone marrow-derived progenitor cells on functional left ventricular contractile recovery post-AMI as well as on long-term mortality and morbidity. Third, there are small risks associated with the interventions required for BM-MNC therapy, though these have been evaluated as acceptable in the risk/benefit assessment for the cell therapy group.

As mentioned previously, the results of previous phase II trials have been inconsistent with regard to efficacy and potential reasons for this include heterogeneity in study design and cell isolation protocols. An important aspect of the BAMI trial has been standardization of the cell processing (using multiple core lab facilities) and intracoronary infusion techniques. For example, bivalirudin is recommended for peri-procedural anticoagulation during infusion, in view of recent data demonstrating impaired migration and homing function of BM-MNCs exposed to heparin. Also, the infusion procedure will be performed within 2–8 days after AMI in all patients as this appears to be the most efficacious time-point from meta-analysis. The trial has been designed using the intracoronary rather than intramyocardial infusion method based on existing data (Supplementary material online, Table S3) and the concerns of ventricular perforation using the currently available percutaneous intramyocardial injection systems at the time of AMI.

Finally, objective unbiased measurement of LVEF in the Echocardiography Core Lab after web-based transmission will ensure that only patients with LVEF ≤ 45% will be included in order to select for high-risk survivors of AMI.

The BAMI trial is therefore an ambitious venture but with a robust study design which addresses the limitations of the previous smaller phase II trials. Hard clinical outcome data have been lacking in this field and this trial will for the first time provide an answer as to whether BM-MNC therapy lowers mortality following AMI.

**Conclusions**

The pivotal BAMI study will be the largest study of BM-MNCs in patients with impaired left ventricular systolic function following successful reperfusion for acute STEMI. The objective of the trial is simple with a single primary endpoint aiming to detect a 25% reduction in all-cause mortality with BM-MNC therapy. The results of the BAMI trial will be highly anticipated, as the field of regenerative therapy will finally have an appropriately sized trial to provide an answer for the most important clinical outcome of all.

**Supplementary Information**

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** BAMI protocol.

**Appendix S2.** BAMI trial logistics - current trial and recruitment status.

**Table S1.** BAMI trial endpoints.

**Table S2.** BAMI trial inclusion and exclusion criteria.

**Table S3.** Clinical trials of stem cell therapy in acute myocardial infarction.

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**Conflict of interest:** A.H.-N. is an employee of t2cure, which licensed the cell product used in the trial. B.A. reports grants from LOEWE (Landes-Offensive zur Entwicklung Wissenschaftlich-ökonomischer Exzellenz) Center for Cell and Gene Therapy (State of Hessen), during the conduct of the study; grants and personal fees from St Jude Medical, personal fees from Novartis, Servier, Boehringer-Ingelheim, Pfizer, outside the submitted work. J.H. reports grants from State (Finland) Research Fund (to institution) during the conduct of the study. S.D. reports grants from null during the conduct of the study; grants, personal fees, non-financial support and other from St Jude Medical, outside the submitted work. In addition, S.D. has a patent null licensed and is a Founder and shareholder of t2cure. All other authors have nothing to disclose.

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