Selected Summaries

Redirecting stem cell therapy

Bartunek J, Behfar A, Dolatabadi D, Vanderheyden M, Ostojic M, Dens J, El Nakadi B, Banovic M, Beleslin B, Vrolix M, Legrand V, Vrints C, Vanoverschelde JL, Crespo-Diaz R, Homsy C, Tendera M, Waldman S, Wijns W, Terzic A. (Cardiovascular Center Aalst, OLV Hospital, Aalst, Belgium; Center for Regenerative Medicine and Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA; Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium; Cardiology Clinic, Clinical Center of Serbia, Medical School, University of Belgrade, Belgrade, Serbia; Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; Department of Cardiology, Centre Hospitalier Universitaire de Liège, Liège, Belgium; Department of Cardiology, University Hospital Antwerp, Edegem, Belgium; Division of Cardiology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; Cardio Biosciences, Mont-Saint-Guibert, Belgium; 3rd Division of Cardiology, Medical University of Silesia, Katowice, Poland; and the Department of Pharmacology and Experimental Therapeutics, Department of Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania, USA.) Cardiopoietic stem cell therapy in heart failure: The C-CURE (Cardiopoietic stem Cell therapy in heart failURE) multicenter randomized trial with lineage-specified biologics. *J Am Coll Cardiol* 2013;**61:**2329–38.

SUMMARY

Stem cell therapy is considered to be a promising regenerative treatment which reverses parenchymal loss in heart failure. C-CURE (Cardiopoietic stem Cell therapy in heart failURE) is a multicentre, randomized, open, prospective trial with lineage-specified biologics that sought to primarily evaluate the feasibility and safety of autologous bone marrow-derived and cardiogenically oriented mesenchymal stem cell therapy and to look for evidence of efficacy in patients with chronic heart failure of ischaemic origin.

Patients between 18 and 75 years of age with ischaemic heart failure (with impaired left ventricular ejection fraction [LVEF]: 15%–40%) were enrolled. The key exclusion criteria were previous cell therapy, ventricular aneurysm, myocardial infarction or revascularization within 2 months before recruitment, moderate-to-severe aortic valve disease or left ventricular thrombus, patients who received a biventricular pacemaker within 6 months and ventricular wall thickness <5 mm in the target area demonstrated by echocardiography done after obtaining consent and before randomization. The efficacy parameters were assessed at 6 months which included left ventricular function, New York Heart Association (NYHA) functional class, quality of life, exercise and peak oxygen capacity, left ventricular dimension, and ejection fraction, along with hospitalization and mortality.

For C-CURE, 319 patients were screened, of which 47 were randomized through a site-independent centralized process: 15 patients were in the control arm and 32 in the treatment arm. Eleven patients from the treatment arm were excluded for various reasons including if sufficient bone marrow cells could not be grown from their extracted marrow. The trial was conducted at nine clinical sites in Europe (Belgium, Serbia and Switzerland) for a span of 3 years. Baseline data depicted similar distribution of demographic attributes. It was a parallel two-arm study in a stable heart failure population with a history of myocardial infarction in which the control arm received standard care in accordance with practice guidelines for heart failure management and patients in the cell therapy arm received bone marrow-derived cardiopoietic stem cells in addition to standard care.

In the cell therapy arm, isolated mesenchymal cells from the bone marrow were exposed to cardiogenic factors including fibroblast growth factor-2, bone morphogenic protein, transforming growth factor-β, activin A, cardiotrophin and α-thrombin. Cells were centrally manufactured at a single, accredited, good manufacturing practice facility supporting trial sites. The stem cell yield obtained after exposure to a cocktail of factors met the pre-specified dose range (600×10^6 to 1200×10^6 cells) required for inclusion in the cell therapy arm. In this study, the autologous mononuclear bone marrow cells were implanted into the myocardium of patients guided by electromechanical mapping with a percutaneous catheter (NOGA XP™), the use of which has been validated by previous studies as well.[1] Cells were injected into mapped areas over 1 minute per injection, with an average of 18 injections per patient spread homogeneously while avoiding apical regions and scars. Overall, 75% success rate was achieved in delivering the processed cells.

Improvement in LVEF was noticed in patients of the cell therapy arm (from 27.5±1.0% to 34.5±1.1%) *v.* control (from 27.8±2.0% to 28.0±1.8%, p<0.0001) and was associated with a reduction in left ventricular end-systolic volume (–24.8±3.0 ml *v.* –8.8±3.9 ml, p<0.001). The cell therapy arm also had improved results in the 6-minute walk test distance (+62±18 m *v.* –15±20 m, p<0.01) with a difference of 77 m in the cell therapy and control arms. *Post-hoc* analysis which included evaluation of composite clinical score encompassing cardiac parameters in aggregation with NYHA functional class, quality of life, hospitalization, physical performance, hospitalization and event-free survival showed benefits for those receiving stem cells. Thus, it was concluded that lineage-guided stem cell therapy was safe and feasible with an immense scope of improvement in patients.

COMMENT

This is the first trial to show the application of guided stem cells for targeted regeneration of a failing organ. It shows the feasibility of lineage priming of bone marrow stem cells from patients with ischaemic heart failure. Administration of derived autologous cardiopoietic stem cells into the hibernating myocardium of patients with heart failure was proven to be safe as the results were encouraging. The study showed improvement of the LVEF with cardiopoietic stem cell therapy compared with standard of care. By introducing lineage guidance into the cell therapy protocol, the C-CURE trial provides initial clinical evidence of a new approach to cardiovascular regenerative medicine.

The hypothesis of this study was based upon the positive results of a preclinical study[2] on murines in which bone marrow-derived human mesenchymal stem cells (MSC; from patients with ischaemic heart disease undergoing coronary artery bypass surgery) were injected into the anterior wall of the left ventricle of mice after guided cardiopoiesis through recombinant cardiogenic cocktail factors. A saline-treated group went through the same procedure. Follow-up was done and it was concluded that despite non-cardiac derivation of stem cells compared with unguided counterparts, cardiopoietic hMSC delivered into infarcted

myocardium showed improved functional and structural benefit without adverse side-effects.

The first ever clinical stem cell trial was conducted by Orlic *et al*.[3] which concluded that locally delivered bone marrow cells can generate *de novo* myocardium, thus improving the outcome of patients with coronary artery disease. A large number of studies based on stem cell injection have indicated the benefits of using stem cell therapy for myocardium repair and improved function irrespective of the type and number of cells. Conventional treatment modalities fail to address parenchymal loss effectively. The C-CURE trial results have provided an innovative direction towards regeneration of the injured myocardium.

The study has certain limitations. Changes in the myocardial regeneration or perfusion were not assessed because of the non-availability of investigations such as MRI and PET at all sites of the trial. Only echocardiography was used for ventricular function assessment and it has a lot of variation. The overall amelioration shown by the majority of previous studies is 3%–5% in ejection fraction with unprocessed cells. C-CURE reported statistically significant results with 7% absolute improvement in ejection fraction over baseline in 6 months in the treatment arm and this is much more than in previous studies. A longer follow-up will show whether the benefit is sustained beyond 2 years. A previous randomized but not placebo-controlled study (BOOST), reported that functional benefit seen at 6 months[4] was not sustained at 18 months.[5]

MSC (which are marrow stromal cells that have the properties of stem cells with a potential to give rise to fat, bone and cartilage) were directed to the targeted area by direct injection with electromechanical mapping using NOGA rather than by the intracoronary method which is an added advantage as shown by previous studies.[6,7] It is believed that the beneficial effect of MSCs has shifted from differentiation into new cardiomyocytes to secretion of paracrine factors. Also, enhancing the properties of bone marrow cells by exposure to a cocktail of factors provided an extensive yield of $>600\times10^6$ cells (with 75% success in 21 patients) which is a step into a new research domain. Whether the higher dose or enhancing the properties of MSCs leads to improvement in ejection fraction again needs an answer.

Another limitation of this trial was that patients were excluded on the basis of not matching up to the release benchmark of cells. This could lead to a probable bias. Since it was a trial to determine the efficacy and the safety of autologous bone marrow-derived stem cells, it would be justified to conduct an intention-to-treat analysis but the details of the excluded patients remain elusive. Nonetheless, the outcome of the study has been encouraging which has resulted in phase 3 trials including CHART-1 which would be focusing on patients with ischaemic heart failure.

Relevance to healthcare in India

The burden of heart failure in India is estimated to be approximately 22.7 million.[8] The numbers are likely to increase in the coming years. Conventional pharmacological treatment modalities undoubtedly improve the clinical status of the heart but they need to be complemented with advanced technologies. Stem cells are seen as a novel therapy for patients with heart failure especially those in whom other methods of treatment are failing. In India, various clinical trials have established the benefits of stem cell technique in which cells were surgically implanted or directed via the coronary artery.[9–11] The preliminary results of the studies have suggested advantages of using stem cells in such patients.

Hence, the C-CURE study seems to be a breakthrough for Indian patients as well. Large-scale trials are being planned in India to quantify the preliminary outcome of successful injection of stem cells in patients. The lineage-directed culturing of MSCs done in this trial is possible in India because of the existence of laboratories with good manufacturing practices. Second, electromechanical mapping was assisted by NOGA XP system with an 8-F Myostar catheter in the C-CURE study. Though this mapping system is not available in India, it can be procured if sustained positive results are obtained from future research work.

In summary, this trial represents a new direction in research where stem cells are guided to grow towards a particular lineage to enhance the effect of therapy. Results of more such trials are awaited.

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