JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 68, NO. 7, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.05.053

Bioabsorbable Intracoronary Matrix for Prevention of Ventricular Remodeling After Myocardial Infarction

Sunil V. Rao, MD,[a] Uwe Zeymer, MD,[b] Pamela S. Douglas, MD,[a] Hussein Al-Khalidi, PhD,[a] Jennifer A. White, MS,[a] Jingyu Liu, PhD,[c] Howard Levy, MD, PhD,[c] Victor Guetta, MD,[d] C. Michael Gibson, MD,[e] Jean-Francois Tanguay, MD,[f] Paul Vermeersch, MD,[g] Jérôme Roncalli, MD, PhD,[h] Jaroslaw D. Kasprzak, MD,[i] Timothy D. Henry, MD,[j] Norbert Frey, MD,[k] Oscar Kracoff, MD,[l] Jay H. Traverse, MD,[m] Derek P. Chew, MBBS,[n] Jose Lopez-Sendon, MD,[o] Reinilde Heyrman, MD,[c] Mitchell W. Krucoff, MD[a]

ABSTRACT

BACKGROUND Bioabsorbable cardiac matrix (BCM) is a novel device that attenuates adverse left ventricular (LV) remodeling after large myocardial infarctions in experimental models.

OBJECTIVES This study aimed to analyze whether BCM, compared with saline control, would result in less LV dilation and fewer adverse clinical events between baseline and 6 months.

METHODS In an international, randomized, double-blind, controlled trial, 303 subjects with large areas of infarction despite successful primary percutaneous coronary intervention (PCI) of ST-segment elevation myocardial infarction (STEMI) were randomized 2:1 to BCM or saline injected into the infarct-related artery 2 to 5 days after primary PCI. The primary outcome was mean change from baseline in LV end-diastolic volume index (LVEDVI) at 6 months. Secondary outcomes included change in Kansas City Cardiomyopathy Questionnaire score, 6-minute walk time, and New York Heart Association functional class at 6 months. The primary safety endpoint was a composite of cardiovascular death, recurrent MI, target-vessel revascularization, stent thrombosis, significant arrhythmia requiring therapy, or myocardial rupture through 6 months.

RESULTS In total, 201 subjects were assigned to BCM and 102 to saline control. There was no significant difference in change in LVEDVI from baseline to 6 months between the groups (mean change ± SD: BCM 14.1 ± 28.9 ml/m^2 vs. saline 11.7 ± 26.9 ml/m^2; p = 0.49). There was also no significant difference in the secondary endpoints. The rates of the primary safety outcome were similar between the 2 groups (BCM 11.6% vs. saline 9.1%; p = 0.37).

CONCLUSIONS Intracoronary deployment of BCM 2 to 5 days after successful reperfusion in subjects with large myocardial infarction did not reduce adverse LV remodeling or cardiac clinical events at 6 months. (IK-5001 for the Prevention of Remodeling of the Ventricle and Congestive Heart Failure After Acute Myocardial Infarction [PRESERVATION I]; NCT01226563) (J Am Coll Cardiol 2016;68:715–23) © 2016 by the American College of Cardiology Foundation.

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From the [a]Duke Clinical Research Institute, Durham, North Carolina; [b]Herzzentrum Luwidshafen, Ludwigshafen, Germany; [c]Bellerophon Therapeutics Inc., Hampton, New Jersey; [d]Sheba Tel Ha Shomer Hospital, Tel Ha Shomer, Israel; [e]Beth Israel Deaconess Medical Center, Boston, Massachusetts; [f]Montreal Heart Institute, Montreal, Quebec, Canada; [g]Free University, Brussels, Belgium; [h]Rangueil University Hospital, Toulouse, France; [i]Medical University of Lodz, Lodz, Poland; [j]Cedars-Sinai Heart Institute, Los Angeles, California; [k]Universitätsklinikum Schleswig-Holstein, Campus Kiel Klinik für Kardiologie und Angiologie, Kiel, Germany; [l]Kaplan Medical Center, Rehovot, Israel; [m]Minneapolis Heart Institute, Minneapolis, Minnesota; [n]Flinders University, Adelaide, South Australia, Australia; and the [o]Hospital Universitario La Paz, Madrid, Spain. The PRESERVATION I trial was funded by Bellerophon Therapeutics Inc. Three former Bellerophon employees participated as coauthors (Drs. Liu, Levy, and Heyrman). Dr. Rao has received research funding from Bellerophon Therapeutics Inc. Dr. Zeymer has received honoraria for participation at steering committee meetings of PRESERVATION I. Dr. Douglas has received research funding from Bellerophon Therapeutics Inc. Dr. Levy is a contractor for and was a consultant to Bellerophon Therapeutics Inc. during the conduct of this study; and owns stock options in the company. Dr. Gibson has received research funding from Bellerophon Therapeutics Inc.

ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional

6MWT = 6-minute walk test

BCM = bioabsorbable cardiac matrix

ECM = extracellular matrix

HF = heart failure

KCCQ = Kansas City Cardiomyopathy Questionnaire

LV = left ventricle/ventricular

LVEDVI = left ventricular end-diastolic volume index

MI = myocardial infarction

NYHA = New York Heart Association

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysi In Myocardial Infarction

Despite reduced mortality via timely intervention and antithrombotic therapies, some patients still experience large ST-segment elevation myocardial infarctions (STEMI) related to delayed presentation, unsuccessful reperfusion, microvascular obstruction, or reperfusion injury. Such patients subsequently experience pathological left ventricular (LV) remodeling associated with functional impairment and chronic heart failure (HF). This is also the result of extracellular matrix (ECM) degradation with loss of tissue integrity, which leads to thinning of the infarct zone. In this setting, specific anatomic features such as higher left ventricular end-diastolic volume index (LVEDVI) are associated with adverse prognosis (1,2). Thus, LV pathological remodeling contributes independently to HF progression. Once HF manifests, the mortality rate is 25% to 30% within 1 year and 50% within 5 years (3). Therefore, preventing LV remodeling after STEMI has the potential to reduce HF and improve survival.

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Two events occur in the setting of large myocardial infarctions (MIs): apoptosis and ECM degradation with high concentrations of extracellular ionized calcium. One novel strategy to prevent pathological remodeling leverages an injectable bioabsorbable alginate, or *bioabsorbable cardiac matrix* (BCM), which provides temporary structural support to the infarct zone until mature fibrotic tissue develops (4). Alginate is derived from seaweed and has been widely used in medical applications and foodstuffs. A small study of direct intramyocardial injection of the alginate polymer Algisyl (LoneStar Heart, Inc., Dallas, Texas) via thoracotomy in patients with advanced HF demonstrated improved exercise capacity, symptoms, and clinical outcomes at 12 months (5). Because BCM can extravasate through permeable capillaries to reach the extracellular space, it can be administered intravascularly. In the presence of ionized calcium present in apoptotic tissues, BCM cross-links into a flexible biological ECM-like scaffolding that creates a cast for the tissue and is gradually and completely degraded and excreted through the kidneys in 3 to 6 months. In preclinical STEMI models, BCM replaced damaged ECM; structurally supported damaged tissue; prevented local dyskinesis; and increased LV thickness, which led to reduced wall stress, improved LV function, and prevention of progressive pathological remodeling (6).

We conducted the PRESERVATION I (Prevention of Remodeling of the Ventricle and Congestive Heart Failure After Acute Myocardial Infarction) trial to determine the safety and effectiveness of intracoronary deployment of BCM on measures of LV remodeling, clinical outcomes, and functional status in patients with large infarctions several days after successful primary or rescue percutaneous coronary intervention (PCI) for STEMI. We hypothesized that BCM, compared with saline control, would result in less LV dilation and fewer adverse clinical events between baseline and 6 months.

METHODS

PRESERVATION I was a multicenter, randomized, double-blind, placebo-controlled trial. Design details have been published (7). National and institutional regulatory authorities and ethics committees approved the trial design, and all subjects provided written informed consent. Trial committee members and investigators are listed in the Online Appendix.

BCM is an aqueous mixture of 1% sodium alginate and 0.3% calcium gluconate. It is a sterile, colorless liquid that is not cytotoxic or mutagenic. Its mechanism of action involves assembling into a flexible gel that structurally resembles ECM when exposed to excess ionized calcium present in infarcted myocardium (8). BCM is designated as a medical device as defined by the U.S. Food and Drug Administration and other participating regulatory authorities.

Dr. Tanguay's institution received payment from the Duke Clinical Research Institute for the PRESERVATION I trial; and he has received funding as a steering committee member; and has received a research grant from Ikaria-Bellerophon. Dr. Kasprzak has received investigator fees from Bellerophon Therapeutics Inc. Dr. Henry is a steering committee member for the PRESERVATION I study. Dr. Chew has received speaker honoraria from Medscape and AstraZeneca. Dr. Lopez-Sendon has received research grants from Daiichi-Sankyo, GSK, Servier, Sanofi, Novartis, the Menarini Group, Pfizer, Merck, and AstraZeneca; and has been an advisor for or received honoraria from Amgen, the Menarini Group, Merck, Servier, Sanofi, Novartis, and AstraZeneca. Dr. Heyrman was an employee of Ikaria-Bellerophon at the time of the study; and owns stock in Bellerophon Therapeutics Inc. Dr. Krucoff has received research grant support from Bellerophon Therapeutics Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 7, 2016; accepted May 10, 2016.