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Research Paper

First-in-man Safety and Efficacy of the Adipose Graft Transposition Procedure (AGTP) in Patients With a Myocardial Scar

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ABSTRACT

Background: The present study evaluates the safety and efficacy of the Adipose Graft Transposition Procedure (AGTP) as a biological regenerative innovation for patients with a chronic myocardial scar.
Methods: This prospective, randomized single-center controlled study included 10 patients with established chronic transmural myocardial scars. Candidates for myocardial revascularization were randomly allocated into two treatment groups. In the control arm (n = 5), the revascularizable area was treated with CABG and the non-revascularizable area was left untouched. Patients in the AGTP-treated arm (n = 5) were treated with CABG and the non-revascularizable area was covered by a biological adipose graft. The primary endpoint was the appearance of adverse effects derived from the procedure including hospital admissions and death, and 24-hour Holter monitoring arrhythmias at baseline, 1 week, and 3 and 12 months. Secondary endpoints of efficacy were assessed by cardiac MRI.
Findings: No differences in safety were observed between groups in terms of clinical or arrhythmic events. On follow-up MRI testing, participants in the AGTP-treated arm showed a borderline smaller left ventricular end systolic volume (LVESV; p = 0.09) and necrosis ratio (p = 0.06) at 3 months but not at 12 months. The AGTP-treated patient with the largest necrotic area and most dilated chambers experienced a noted improvement in necrotic mass size (−10.8%), and ventricular volumes (LVEDV: −55.2 mL and LVESV: −37.8 mL at one year follow-up) after inferior AGTP.
Interpretation: Our results indicate that AGTP is safe and may be efficacious in selected patients. Further studies are needed to assess its clinical value. (ClinicalTrials.org NCT01473433, AdiFlap Trial).

1. Introduction

Cardiovascular disease remains the most common cause of mortality worldwide, accounting for more than 17 million deaths annually (Anon., 2011). Myocardial infarction (MI) leads to irreversible myocardial sequelae, often causing debilitating symptoms and shortening life span. Recently, biological regenerative innovations have been introduced as promising therapeutic options (Soler-Botija et al., 2012; Gálvez-Montón et al., 2013a; Prat-Vidal et al., 2014).

Cardiac fat contains a population of mesenchymal-like progenitor cells capable of differentiating into cells that closely resemble cardiomyocytes, both morphologically and molecularly. In murine MI models, these cells improved cardiac function parameters and promoted local neoangiogenesis under hypoxia (Bayes-Genis et al., 2010). The adipose tissue surrounding the heart and pericardium may serve as an autologous biological matrix for salvaging injured myocardium.

The Adipose Graft Transposition Procedure (AGTP) uses patient's existing cardiac fat directly, placing it over the myocardial infarcted zones, rather than explanting a cardiac adipose biopsy to retrieve the cells (Gálvez-Montón et al., 2011; Gálvez-Montón et al., 2013b). In the

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acute MI porcine model, functional analyses showed an improvement in LVEF in the AGTP-treated arm five-fold higher than untreated animals (Gálvez-Montón et al., 2011). In the chronic MI porcine model, morphometry revealed a 34% reduction in left ventricular infarct area of AGTP-treated relative to control animals (Gálvez-Montón et al., 2013b). These preclinical studies in a large mammal model suggest that AGTP may be an effective post MI treatment for patients. Accordingly, a prospective randomized trial was set up to assess safety and efficacy of AGTP in patients with a myocardial scar.

2. Patients and Methods

2.1. Patients

The study included 10 candidates for myocardial revascularization with an established chronic transmural myocardial scar, from January 2012 to November 2013. Inclusion criteria included patients ≥18 years of age, with an established transmural MI (minimum three months old) anatomically non amenable for surgical revascularization, and candidates for coronary artery bypass graft (CABG) surgery of other arteries non responsible for the transmural scar. A non-revascularizable area was defined as a chronic transmural necrosis detected by means of late gadolinium enhancement >70% of myocardial thickness on MRI.

Exclusion criteria were: severe valvular disease apt for surgery, candidates to surgical ventricular remodeling, contraindication for MRI, extra-cardiac disease with life expectancy <1 year, severe renal or hepatic insufficiency, previous cardiac surgery, very high surgical risk by EuroSCORE (>8), and pregnant or breastfeeding women.

2.2. Study Design and AGTP Intervention

This study was a prospective, single-center, randomized controlled phase I—II clinical trial (ClinicalTrials.gov number NCT01473433, AdiFLAP Trial). It was designed and implemented in accordance with the Declaration of Helsinki; informed consent was obtained from all participating patients.

Enrolled patients were randomly allocated in 2 arms (Fig. 1):

- Control arm (n = 5): Patients in whom the revascularizable area was treated with CABG and the non-revascularizable area was left untouched.
- AGTP-treated arm (n = 5): Patients in whom the revascularizable area was treated with CABG and the non-revascularizable area was covered by an autologous pericardial adipose graft. Fig. 2 summarizes the steps of the AGTP intervention. First, to obtain the graft, the pericardial adipose tissue was detached with its vascularization intact (depending on scar location, the adipose tissue was detached from the left or the right side of the pericardium as needed); next, after pericardiotomy, the vascular adipose graft was gently positioned to ensure full coverage of the necrotic zone; finally, to secure the flap, the edges were adhered to bordering healthy myocardium with commercially available cyanoacrylic-based surgical glue (Glubran®2, USA) (Gálvez-Montón et al., 2011; Gálvez-Montón et al., 2013b; Bagó et al., 2013; Roura et al., 2015).

The clinical cardiologist handling postsurgical care and the MRI specialist were both blind to the participants' treatment. Study visits consisted of a baseline visit (obtained informed consent and performed clinical assessment, including MRI), surgical intervention, and follow-up visits at one week (clinical assessment), three and 12 months (clinical assessment including MRI) after procedure.

Safety of the procedure was evaluated by the presence of major clinical events including hospital admissions and death, and by the results of a 24-hour Holter monitor test done at each study visit to assess arrhythmias. Efficacy was assessed by left ventricular ejection fraction (LVEF), cardiac output (CO), stroke volume (SV), end-diastolic wall mass (EDWM), left ventricular end-diastolic (LVEDV) and end-systolic volume (LVESV) by means of cardiac-MRI. NTproBNP, troponin I (TnI), NYHA functional class and Framingham derived clinical score were also assessed.

2.3. Cardiac MRI Data Acquisition and Analysis

All imaging were performed in a state-of-the-art 1.5 T clinical imaging system (Avanto; Siemens Medical Imaging, Erlangen, Germany) with the patient in the supine position and a 16-element phased-array coil placed over the chest. Images were acquired during breath-holds with ECG gating. We used a segmented k-space steady-state free-precession sequence [RT 44.70 ms; echo time 1.26 ms; flip angle 78; matrix 272; spatial resolution (1.3–1.5)×(1.3–1.5) × 8 mm depending on the field of view] for cine imaging in parallel short-axis (contiguous slices of 8-mm thickness covering from base to apex) and 3 long-axis views of the left ventricle. Delayed enhancement images were acquired with a segmented gradient-echo inversion-recovery sequence [RT (600–800) ms depending on the cardiac heart rate; echo time 3.24 ms; flip angle 25; matrix 256; spatial resolution 1.3 × 1.3 × 8 mm] at matching cine-image slice locations 10 to 20 min after intravenous gadolinium-DTPA administration (0.20 mmol/kg; Gadovist, Bayer Schering Pharma AG, Berlin, Germany) (Simonetti et al., 2001). We optimized the inversion time to null the normal myocardium and adjusted views per segment and trigger delay according to the patient's heart rate. Native and post contrast cardiac T1 mapping was calculated using a modified Look–Locker inversion recovery sequence (MOLLI) in a short axis view at the infarct level (Moon et al., 2013; White et al., 2013; Messroghli et al., 2004, 2007).

All images were reviewed and analyzed off-line with a specialized post-processing software (QMass-MR, v.7·0; Medis Medical Imaging

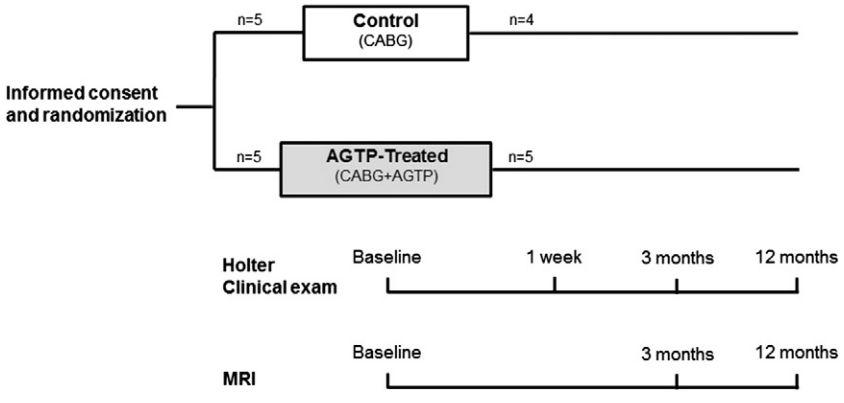

Fig. 1. Study design. n: number of patients, CABG: coronary artery bypass graft, AGTP: Adipose Graft Transposition Procedure, MRI: magnetic resonance imaging.