P5676

Safety and immunomodulatory action of epicardial patches combined with allogeneic adipose-derived mesenchymal stem cells in a rodent and porcine model of myocardial infarction

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The long-term benefit of epicardial collagen scaffolds seeded with autologous adipose derived-mesenchymal stem cells (Cg-ADSC) has been previously shown in rat and pig models of chronic myocardial infarction (MI). In contrast to direct intramyocardial administration of ADSC, epicardial delivery using collagen scaffolds enhanced stem cell engraftment and improved cardiac function, which was mediated through a decrease on myocardial remodeling and an increased vasculogenesis. In order to get into the clinical scenario, collagen scaffolds were seeded with allogeneic ADSC and manufactured under GMP standards. Their safety was confirmed under GLP conditions in different rodent models of tumorogenecity, biodistribution and toxicity and their putative immunogeneic action analyzed in a pig chronic MI model. All the animal studies were performed according to the principles of laboratory animal care. Thus, tumorogenicity was evaluated in Rag2-/-gc-/- immunodeficient mice subcutaneously implanted with the cellularized patch. No tumoral or differentiated cells were detected after 3 and 8 months of implantation (n=10/group). Also, ADSC distribution was shown to be confined to the cardiac tissue when implanted in the infarcted rat hearts. Cells were no detected in reproductive organs or brain (among other organs) 7 or 30 days post-implant (n=5/group). Importantly also, toxicity studies showed no adverse effects 2, 10, 30 and 90 days post-implantation in infarcted and healthy Nude rats (n=6/group). Clinical biochemistry, hematological and coagulation blood parameters together with urine analysis did not show significant changes. Necropsy and anatomopathological analysis did not reveal significant alterations due to the patch, neither.

Next, the inflammatory and immune response towards the allogeneic patch was analyzed in chronically infarcted pigs implanted with 50 million ADSC injected or implanted in combination with the collagen scaffold. Untreated infarcted animals were included as control group (n=8/group). The immune response was analyzed before implantation and 15, 30 and 90 days post-implant, determining the evolution of lymphocyte populations, monocytes, granulocytes and leukocytes in blood as well as levels of immunoglobulins and serum proteins. No significant changes were globally detected in any of the parameters analyzed. Moreover, blood biochemical parameters indicated a well preserved hepatic and renal function in all groups thorough the study.

In conclusion, treatment of the heart with an allogeneic Cg-ADSC patch is a safe treatment and do not induce an adverse inflammatory reaction, which could be a promising therapy for the treatment of ischemic patients.

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P5677

The long-lasting symptomatic benefit induced by lung ultrasound-guided therapeutic thoracentesis in refractory congestive heart failure: a retrospective cohort study

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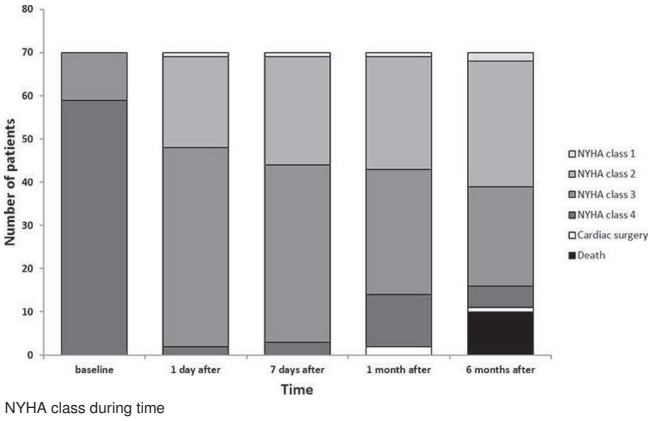
Background: Pleural effusion refractory to diuretic treatment is frequent in advanced congestive heart failure (HF). Therapeutic thoracentesis (TT) is a time-honored practice, recently made simpler and safer by guidance with lung ultrasound (LUS).

Purpose: To assess the feasibility and clinical impact of LUS-driven TT in refractory HF.

Methods: In a retrospective analysis of a single center 10 years (2007–2017) experience, we recruited 373 patients (180 females, age 69.5±12.4 yrs) with: 1. HF with reduced ejection fraction (26±12%, by 2D echo, modified biplane Simpson method); 2. NYHA class ≥3; 3. Maximal tolerated medical therapy (mean furosemide dose 191±173 mg); 4. Pleural effusion ≥ moderate at LUS, with maximal interpleural space >20 mm (sitting position, subscapular to midaxillary line).The underlying cause of HF was post-ischemic (32.9%) or idiopathic (41.4%) cardiomyopathy, severe aortic stenosis-regurgitation (14.3%), severe mitral regurgitation-stenosis (11.1%) and repaired congenital defect (0.3%). NT-BNP (available in 14 patients) was 12,717±4,575 pg/mL at study entry. All patients underwent LUS-guided therapeutic thoracentesis (TT). Medium-term follow-up information was available in 70 patients. Nineteen patients also underwent six-minute walk test (6MWT) before and after TT.

Results: LUS-guided TT was feasible and uneventful (462 procedures, 392 of them right-sided) in all patients. Evacuated pleural fluid by passive drainage was 1030±534 mL (range 200 to 2500). The maximal interpleural space was 73.6±15.6 mm before and 12.4±3.1 mm after TT (p<0.001).TT induced an immediate symptomatic improvement in all patients, with NYHA class decrease from 3.84±0.37 pre- to 2.7±0.55 post-TT (P<0.001). The improvement was short-lived (few hours) in 11%, and long-lasting (for weeks and months) in 89% of patients, in spite of largely unchanged medications (see figure). The 6MWT was 52±29 m before, 117±37 m at 2 hours after, 146±45 m one day after, 262±45 m one week after and 287±56 m one month after TT (p<.001 for all inter-group differences).



NYHA class during time

Conclusion: This single-center, retrospective study demonstrated the efficacy of LUS-driven TT of pleural effusion in decompensated HF patients. TT induces immediate, often dramatic, symptomatic relief usually accompanied by persistent improvement.

P5678

Real world eligibility and prognostic relevance for sacubitril/valsartan in unselected heart failure outpatients: data from an Italian registry (IN-HF outcome)

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Background: Although Angiotensin-Receptor-Neprilysin Inhibitors (ARNI) are recommended by all international guidelines for outpatients with chronic heart failure (CHF) and reduced ejection fraction (EF) who remain symptomatic despite optimal conventional drug treatment, uptake of this proven beneficial therapy in clinical practice takes time. In Italy ARNI are reimbursed by the National Health Service since March 2017 within criteria set by the national Medicines Agency (AIFA) mandating patient inclusion in a dedicated AIFA monitoring registry (AIFA-MR).

Aim and methods: We aimed to assess the eligibility profile for ARNI treatment of CHF patients who had been enrolled in a nation-wide all comers HF outpatient Italian Registry according to the drug's indication criteria from PARADIGM-HF and AIFA-MR, respectively. Discrepancy of inclusion thresholds for NYHA class, LVEF, eGRF and potassium between AIFA-MR and PARADIGM-HF criteria are reported in the figure.

Results: Among 1026 patients enrolled in the registry, ARNI-eligible subjects differed from ineligible ones for younger age, lower proportion of women (16%, p=.003, and 18%, p=.012, vs 25%), and higher proportion implanted an ICD (34%, p<.0001, and 26%, p=.0006, vs 17%) by both AIFA-MR and PARADIGM-HF criteria. ARNI-eligible and ineligible patients by PARADIGM-HF criteria had