Clinical Trial Insight: cell and gene therapy

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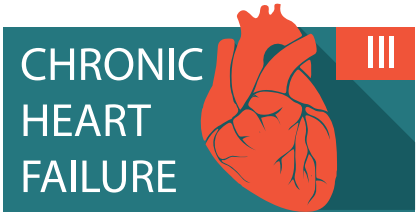
Dr Alexey Bersenev, Yale University, USA, provides an expert overview of the most important clinical trials, cases and cohort studies conducted in academic and industry with particular focus on later-stage efficacy data.



MIXED OUTCOME FOR PHASE 3 CARDIAC CELL THERAPY TRIAL

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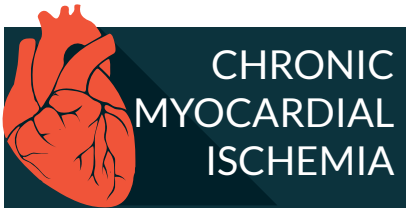
Celyad, a Belgium-based pharmaceutical company, has released headline results [1] of their Phase 3 cardiac cell therapy pan-European trial CHART-1 [2]. Efficacy of autologous bone marrow stem cells induced to cardiac lineage in culture were tested in comparison with sham procedure on 271 patients with chronic ischemic heart failure. Primary endpoints of the study were missed; however, analysis of the trial data identified a 60% patient subpopulation who did meet the primary endpoints. Celyad's press release has a positive spin and some media outlets called the results of the trial "mixed" or even "positive". Identification of the patient subgroup that could potentially benefit from the therapy, may contribute to the design of CHART-2 trial in USA and may lead to discussions with EMA in Europe about potential commercialization. In line with this, Celyad will seek a partner to accelerate further development and commercialization. Unfortunately for Celyad, the company's value dropped by more than a third, which will make the search for a potential partner more difficult.

NEURAL STEM CELL TRIAL TERMINATED

US-based company StemCells Inc. has announced termination of their Phase 2 neural stem cell trial in patients with spinal cord injury [3] and as a consequence, the company will stop its operations. This decision was made at the end of May 2016, after a review of preliminary data obtained from their ongoing "Pathway Study". 17 patients received the stem cell-based intervention in the trial so far, without significant safety issues. Despite some positive efficacy trends being observed in the first cohort of patients (cervical level) a few months after treatment, the "magnitude of the effect... did not justify continuing the study" according to the company press release.



CYTORI PUBLISHED RESULTS FROM THE TERMINATED ATHENA TRIALS

Regenerative medicine company Cytori had two cardiac cell therapy trials ATHENA, which were terminated last year, due to safety concerns and business considerations. Recently, the company has published available data generated from both trials [4]. 31 patients were included in the analysis (28 from ATHENA 1 [5] and three from ATHENA 2 [6]) – 17 in the cell therapy group and 14 in placebo. Patients with chronic myocardial ischemia received 40 or 80 millions of autologous adipose tissue-derived stromal vascular fraction cells, processed from lipoaspirates at the point of care with Celution system. Serious adverse events in two patients, related to procedure but not to the cells, triggered the "stopping rule" and the studies were suspended. Although the FDA allowed the trials to continue after protocol amendments, the company decided to terminate the trials. In relation to safety, ATHENA 1 did not meet the primary endpoint, measured by major adverse cardiac events (MACE): 35.3% in cell therapy group versus 21.4% in placebo. Some efficacy endpoints, specified in ATHENA 2 were met at some time points (for example, Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score), but some were not met (no difference with placebo). The authors concluded that studies were "feasible with suggestion of benefit".

STEM CELL-BASED ALS TRIAL GETS SPONSORSHIP

US-based company NeuralStem has sponsored a phase 2, open-label, dose-escalation trial for fetal neural stem cell transplantation in patients with ALS. The results of the study were published online

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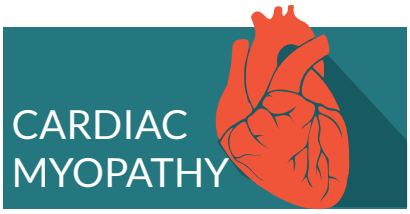
in *Neurology* on June 29, 2016 [7]. 15 patients, divided into five treatments groups underwent experimental procedures in three different US centers. Even though there were two cases of serious adverse events observed and two deaths (attributed to disease progression) before 270 days, the procedure seemed to be safe and well tolerated in general. Of the total 165 reported adverse events, 14 were probably, but not definitely, related to the stem cells. Immunosuppressants caused some side effects, but it was less than that of the surgical procedure. The experimental treatment was not clinically beneficial and as it was highlighted by the investigators, the trial was not designed and powered to assess efficacy; however the absence of clinical impact progression is an important observation. It is not clear at this point how NeuralStem will proceed with further ALS studies.

DISAPPOINTING RESULTS FROM VERICEL'S CARDIOMYOPATHY TRIAL



US-based regenerative medicine company Vericel has published results of their ixCELL-DCM clinical trial [8]. Efficacy of their bone marrow-derived autologous cell therapy Ixmyelocel-T was assessed in patients with ischemic dilated cardiomyopathy. This randomized placebo-controlled study included 126 participants (60 in Ixmyelocel-T and 66 in placebo group) from 31 centers of North America. The study met the primary endpoint, which was composed of "all-cause death, cardiovascular admission to hospital, and unplanned clinic visits". However, secondary efficacy endpoints of the study were not met (no difference compared with placebo). Despite the company's excitement, investors were not impressed by the trial results and have dumped the company's stock on its day of release.

INTERIM DATA ON METACHROMATIC LEUKODYSTROPHY TRIAL SHOWS PROMISE

Researchers from San Raffaele Scientific Institute-TIGET (Italy) reported results [9] of ad-hoc analysis of their cell–gene therapy trial [10] for the fatal demyelinating disease – metachromatic leukodystrophy. Autologous hematopoietic progenitor $CD34^+$ cells were transduced with lentivirus carrying ARSA (the absent enzyme) gene. All nine children included in the trial survived at the point of data analysis (an average of 36 months). Engraftment of the cells and ARSA activity were detected in all children. Six out of nine patients were able to achieve functional recovery "similar to normally developing children". Overall progression of the disease halted in eight out of nine patients

and demyelination of the CNS has stopped. Long-term outcome analysis will be required to confirm the durability of effects. Pharmacuetical giant GSK is commercializing a number of gene therapy targets from TIGET and this trial is one of their "licensing indications".

GSK'S GENE THERAPY DRUG FOR SCID-ADA RECEIVED EU APPROVAL

On May 27 2016, GSK received European approval for Strimvelis, their stem cell gene therapy designed for the treatment of an inherited form of immunodeficiency: SCID-ADA [11]. The company transferred technology from the Italian institutions, Fondazioine Thelethon and Ospedale San Raffaele. Before this announcement, a group of authors from San Raffaele and GSK published a report [12] which actually supported their EMA approval. Long-term outcomes and quality of life after experimental gene therapy were analyzed in 18 patients with SCID-ADA. Overall survival was 100% in median observation time of 6.9 years. Three out of 18 patients did not respond to gene therapy due to lack of engraftment. No leukemic transformation or other serious adverse events were reported. Metabolic activity (ADA level) and functional recovery of T- and B-cells were durable throughout the observation period.

PHASE 2 MULTIPLE SCLEROSIS CELL THERAPY TRIAL SHOWS POTENTIAL

Canadian researchers have published results [13] of a small, uncontrolled, single arm Phase 2 trial [14], where autologous hematopoietic progenitor cells were transplanted in 24 myeloablated patients with multiple sclerosis. The primary endpoint (3-year disease-free survival) was achieved by 70% of patients (with a median follow-up 6.7 years). These results are really impressive, however, a more aggressive pre-transplant conditioning regime (compared to other similar studies) led to treatment-related toxicity and one case of death. 33% of patients had grade 2 and 58% had grade 1 transplant-related toxicity.

RHEUMATOID ARTHRITIS CELL THERAPY TRIAL FAILS TO MEET EFFICACY ENDPOINTS

Cell therapy company Tigenix has published results [15] of their multicenter, double-blind, placebo-controlled trial [16] for the treatment of refractory rheumatoid arthritis. Allogeneic adipose tissue-derived mesenchymal stromal cells were infused intravenously in three cohorts of patients, at three different doses. 141 adverse events were observed in 53 treated

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patients, but the authors deemed it as a "non-toxic, well tolerated" intervention (primary end points). Interestingly, no direct correlation was observed between the dose and clinical outcome. The lower dose was the most efficacious. Clinical benefit of cells in comparison to placebo was more pronounced at the 3-month time point, measured by functional scales (exploratory efficacy endpoints). However, the study was not powered statistically enough to conclude efficacy between treatment and placebo groups. The authors detected clinically insignificant sensitization against allogeneic cells. Clinical benefit diminished after 3 months post treatment.

A PHASE 2 CARDIAC GENE THERAPY TRIAL DEMONSTRATED MIXED OUTCOME

Results of a Phase 2, randomized, placebo-controlled [17] cardiac gene therapy study, were published this week in *JAMA Cardiology* [18]. The trial assessed efficacy of *AC6* gene transfer through cardiac arteries. *AC6* (adenylyl cyclase type 6) regulates heart muscle function. Not all primary endpoints were met in the trial, therefore I interpret the results as mixed. Only short-term (at 4 months) moderate improvement of heart function was observed. This gene therapy approach is commercialized by Renova Therapeutics

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