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.

ALS INTERIM RESULTS PUBLISHED

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The highly anticipated interim results of a Phase 1/2a cell therapy trial in amyotrophic lateral sclerosis (ALS), have been published in *JAMA* Neurology [1]. This ongoing clinical trial, sponsored by Israeli company BrainStorm Cell Therapeutics, is assessing the efficacy of autologous bone-marrow-derived neurotrophic factor-secreting mesenchymal stem cells. Safety endpoints were met. 87% of patients responded to the cell therapy, demonstrating at least 25% improvement in functional tests at 6 months. Results of this study were portrayed by general media as "groundbreaking", but it is important to emphasize that only 15 out of 26 patients were available for follow-up and statistical post hoc analysis at 6 months post intervention. Two cases of death from disease progression and the group of patients who received intramuscular injections and failed to demonstrate an improvement were excluded from the analysis. Whilst the cell products appear to slow down the progression of ALS, the study was uncontrolled and these results are still preliminary.

DISAPPOINTING OUTCOMES IN CROHN'S PHASE 3 TRIAL

The European Society for Blood and Marrow Transplantation (EBMT) concluded its very important study evaluating the transplantation of autologous hematopoietic stem/progenitor cells in patients with refractory Crohn's disease. The randomized, parallel-group controlled Phase 3 clinical trial [2] was conducted in 11 European centers. Results of the study were published in JAMA [3]. Data analysis included 23 patients in the experimental group and 22 patients in control groups. Unfortunately, the trial has failed to demonstrate efficacy and was terminated due to toxicity.

CORD BLOOD EXPANSION ENHANCED

Different techniques used in the expansion of hematopoietic stem/progenitor cells from cord blood continue to progress through different stages of clinical development. Results of one such study were recently published in Cell Stem Cell [5]. The compound StemRegenin-1 (SR-1), commercialized by Novartis, causes a robust expansion of engraftable cord blood $CD34^+$ cells. In the Phase 1/2 trial, conducted at the University of Minnesota, USA, exposure of cord blood units to SR-1 led to accelerated neutrophil and platelet engraftment in all patients in double-unit cord blood transplant settings. In 65% of patients (11 out of 17), the expanded unit outperformed the unmanipulated unit as measured by engraftment. This indicates that SR-1 can at least maintain true stem cells. On average, SR-1 resulted in a 330-fold increase in $CD34^+$ cells number during *ex vivo* expansion. These results will allow further testing of single expanded units in the near future.

FIRST RESULTS FROM ALLOGENEIC CAR T-CELLS IN B-CELL MALIGNANCIES

There is great interest in the potential application of allogeneic CAR T-cell therapies in oncology, but with little published studies to date. This month, James Kochenderfer from the National Cancer Institute, USA, reported the first data on using allogeneic CD19-CAR T-cells in patients with B-cell malignancies, who had previously undergone hematopoietic stem cell transplantation but with disease progression [6]. CAR T-cells were generated from the same allo donor and infused without conditioning of the recipient. 40% of patients (8 out of 20) achieved remission with the greatest success being seen in acute lymphoblastic leukemia patients (4 out of 5 patients went into complete remission). Remarkably

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no graft-versus-host disease was observed. This study provides evidence for the safety and feasibility of allo-CAR T-cell approach post-stem cell transplant and indicates further investigation is warranted.

SPINAL CORD TRIAL TERMINATED

Another Phase 3 trial failed to meet its efficacy endpoints. South Korean researchers reported results of single intramedullary injection of autologous bone marrow-derived mesenchymal stem cells in patients with chronic spinal cord injury [4]. Only 2 patients out of the 16 analyzed showed functional improvement. The trial, supported by Pharmicell Co, Ltd, was terminated due to futility.

CIRRHOSIS CELL THERAPY TRIAL FAILS TO MEET EFFICACY ENDPOINTS

A double-blind randomized controlled trial was designed by Iranian medical researchers to assess the safety and efficacy of autologous bone marrow mononuclear cells or $CD133^+$ cells versus placebo in patients with decompensated liver cirrhosis [7]. The results of this trial were recently published [8]. Nine of 27 patients were excluded from analysis. From the 18 patients available for analysis, four received $CD133^+$ cells, eight received mononuclear cells and six were assigned to placebo. The low number of patients per group makes the study underpowered for rigorous statistical assessment. The experimental treatment was safe; however, efficacy endpoints were not met at 6 months follow up (no significant difference between the three groups). Some positive trends were transiently observed in the $CD133^+$ group.

ATHERSYS RELEASE 1-YEAR FOLLOW UP DATA

One of the biggest events in the cell therapy field from the last year was the failure of a Phase 2 stroke trial, sponsored by US-based company Athersys [9]. In February 2016, Athersys released an update on the long-term outcomes from this trial. Compared to the 90-day readout reported previously, the difference between MultiStem (allogeneic

multipotent adult stem cells) and the placebo significantly increased by the 1-year time point. The difference between groups was greater in the patients treated within the first 36 hours after stroke. About a month before release of this follow-up, Athersys signed a partnership agreement with Healios to commercialize MultiStem for ischemic stroke in Japan [10].

MODERATE IMPROVEMENT IN T1 DIABETES

A variety of cell types have been assessed for the potential treatment of type 1 diabetes. In a single-center, randomized controlled trial, diabetic patients received a mix of expanded allogeneic Wharton's jelly umbilical cord-derived mesenchymal stromal cells and autologous bone marrow-derived mononuclear cells. According to the published data, metabolic measures (fasting C-peptide) were moderately improved in most patients from the 'cells' group compared to control (standard treatment) at one year follow-up. Cell therapy allowed for a reduction in insulin dosage to 29% in the experimental group [11].

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