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.

GENE THERAPY SHOWS POSITIVE RESULTS IN SMA PATIENTS

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The end of 2017 was a landmark period for the gene therapy field. The results of a small study [1], sponsored by the US-based company AveXis [2], was the most impressive. 15 pediatric patients with spinal muscular atrophy (SMA) were treated with single dose of gene therapy (adeno-associated viral vector with *SMN* gene). Results showed 100% event-free survival at 20 months of age (study cutoff) compared to 8% in historic control. Multiple motor functions were improved in all patients and none of them required permanent mechanical ventilation. Two serious adverse events in two patients were deemed as related to experimental treatment (high levels of serum aminotransferases) and were reversed.

PROMISING OUTCOMES IN TWO HEMOPHILIA TRIALS

Results of two industry-sponsored trials of gene therapy for hemophilia were reported in December 2017. Though tested in a small number of patients, results of both studies look very promising. In the first trial [3], sponsored by Spark Therapeutics [4], nine out of ten hemophilia B patients (with factor IX deficiency) stopped having spontaneous bleeds and eight out of ten patients stopped using factor IX infusions. Importantly, these effects were durable (follow-up 28–78 weeks) for over a year. The second study [5], sponsored by BioMarin Pharmaceuticals [6], showed sustained therapeutic level of factor XIII activity in six out of seven hemophilia A patients (who received higher dose) for over 1 year of observation period. It led to a significant reduction of total number of infusion of factor VIII – from 138 per year before to 2 per year after gene therapy. Both studies utilized adeno-associated virus (though encoding different coagulation factors) and did not report serious adverse events, related to the viral vector.

STEM CELL TRANS-PLANTATION RESULTS FOR SCLERODERMA PUBLISHED

Results of a large academic Phase 2/3 trial (SCOT study) [7] assessing the efficacy autologous CD34 cell transplantation in patients with systemic sclerosis were published in the *New England Journal of Medicine* [8]. This NIH-funded study conducted in 26 sites compared 33 patients in 'CD34 group' versus 37 patients in 'cyclophosphamide group'. Study met both primary and secondary endpoints. CD34 transplantation group was superior in composite score as well as event-free survival and overall survival at 54 and 72 months. Due to the long duration and course of disease, only 27 patients in the 'CD34 group' and 19 patients in the 'cyclophosphamide' group completed the trial. Durable responses to this experimental therapy comes at a cost of toxicity (mostly due to infections and malignancies). In this regard, the authors showed 3 and 6% of treatment-related mortality at 54 and 72 months, respectively. Even though this rate of toxicity is usual for myeloablative conditioning, surprisingly it was lower than the previously reported analogous European trials (ASTIS). If the FDA approves the use of CliniMACS device to isolate CD34 cells for systemic sclerosis patients, the treatment could enter wide clinical use through academic medical centers and large hospitals with expertise of hematopoietic stem cell transplants and management of autoimmune diseases.

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UMBILICAL CORD BLOOD TRANS-PLANTATION FOR CEREBRAL PALSY

Duke University and The Robertson Foundation have reported long-awaited results [9] of the clinical trial [10], which assessed efficacy of autologous cord blood transplantation in children with cerebral palsy. This trial was designed as randomized and placebo-controlled with crossover at 1 year. The study did not meet the primary endpoint – the improvement of gross motor function was not different from placebo at 1 year. However, *post hoc* analysis revealed significant improvement of motor function in children who received higher doses of cord blood cells, compared to lower dose or placebo. The results of this analysis may guide future trial design. Currently, Duke continues to offer this type of experimental treatment under an 'expanded access' program [11].

MSCS HOLD HOPE FOR PATIENTS WITH SEPTIC SHOCK

Based on experimental data, researchers around the world are having high expectations for the potential efficacy of mesenchymal stromal cells (MSC) in therapy of sepsis and septic shock. However, no data have been published thus far. While the large European SEPCELL trial just started enrolment [12], Canadian researchers reported for the first time [13], results of a Phase 1 study [14], where they tested allogeneic freshly cultured MSC in septic shock. This small study, which included nine patients, was designed to assess safety and tolerability of escalated cell doses. Maximal dose of MSCs tested in the trial was 3 million of MSC per kg of body weight with total infused cell number 250 million. Observational cohort, included 21 patients was served as control to experimental MSC cohort. There were no MSC infusion-associated adverse events (first 24 hours post-infusion). Researchers did not observe any difference in prespecified or unexpected adverse events rate between observational and MSC cohorts (time of observation 28 days or until discharge from the hospital). Both cohorts had similar death rates (22%). All MSC doses, included maximal, were well tolerated. Even though the trial confirmed the safety of MSC infusions in patients with septic shock, there were no signals of potential efficacy observed. Safety and feasibility data justify Phase 2 trial.

CAR-T TRIAL RACES ON

Results of two CAR-T trials, sponsored by Kite Pharma [15] and Novartis/University of Pennsylvania [16], were published in December of 2017. Both trials tested safety and efficacy of anti-CD19 CAR-T cells in patients with some types of relapsed/refractory lymphoma. Investigators of Kite's ZUMA-1 trial [15] reported results [17], based on analysis of enrolled 111 patients, including long-term follow-up at 6 and over 12 months. At 6 months, objective response rate was 82% and complete response (CR) was 52%. 40% of patients stayed in CR at median follow-up of 15.4 months. Novartis/Upenn reported outcome [18] of 28 infused patients. Important highlight of this trial is the high dropout rate from intent-to-treat patient population – 27%. The overall response rate at 3 months was 64% and at 6 months – 57%. All patients, who achieved CR by 6 months, stayed in CR for 29.3 months (median). Both studies reported quite high rates of typical toxicities, associated with systemic infusion of CAR-T cells – cytokine release syndrome and neurotoxicity. Overall, three deaths related to CAR-T therapy occurred in in these trials.

ADIPOSE-DERIVED MSCS SHOWS LONG-TERM DURABILITY IN CROHN'S DISEASE PATIENTS

In 2016, Belgian company Tigenix reported efficacy results of their Phase 3 registration trial (ADMIRE-CD) [19], which assessed adipose tissue-derived MSC for local injections in Crohn's disease patients with perianal fistulas. Now, Tigenix is reporting durability of efficacy outcome at follow-up mark of 52 weeks [20]. Combined remission in MSC group was 56.3 versus 38.6% in placebo control. It is about the same remission rates as it was demonstrated previously at 24 weeks. Safety was also maintained at 52 weeks. These durability data are supporting a filing for marketing authorization. Right now, the company is awaiting regulatory decision on European approval.

FOLLOW-UP OF THE FIRST CARDIAC CELL THERAPY TRIAL

Yet another long-term outcome report [21] came out recently from TIME study investigators. The TIME trial [22] tested efficacy of autologous bone marrow mononuclear cells versus placebo in 120

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patients with myocardial infarction. It was the first cardiac cell therapy trial in the USA, sufficiently powered to assess efficacy. The study was completed 5 years ago and reported as failed due to futility. Now, study investigators are reporting 2-year follow-up in 85 patients, mostly based on imaging data (MRI). "Lack of benefit is maintained when measured at 2 years" wrote the authors. Importantly, no safety concerns were observed at the 2-year mark after infusion of bone marrow cells intracoronary.

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