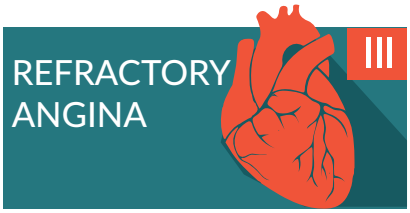
Clinical Trial Insight: cell and gene therapy

Q3 2016

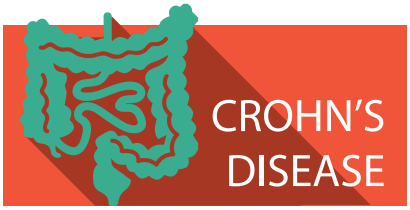
Dr Alexey Bersenev, Yale University, USA, provides an expert overview of the most important clinical trials, cases and cohort studies conducted in academic and industry with particular focus on later-stage efficacy data.



BAXALTA PUBLISH RESULTS FROM TERMINATED RENEW TRIAL

ALEXEY BERSENEV,
Director, Cell Therapy Processing/Advanced Cell Therapy Labs,
Yale University, USA

A Phase 3 clinical trial [1] to assess autologous CD34+ cells in refractory angina was initiated by Baxter Corp. in 2012 and was later managed by its spin off, Baxalta (recently acquired by Shire). A couple of years ago, the company had suspended enrolment and then decided to terminate the trial. Results from this trial have now been published [2].The sponsor terminated the study for strategic considerations after enrolment of 112 of planned 444 patients. The study failed as primary endpoints were not met and some of secondary endpoints were barely met.



TIGENIX AWAITS EMA'S MARKETING APPROVAL FOR ITS PHASE 3 TRIAL

Belgian company Tigenix has published results of its Phase 3 trial [3] aimed at assessing the safety and efficacy of adipose tissue-derived mesenchymal stromal cells in the treatment of perianal fistulas in Crohn's disease patients. It was one of the biggest stem cell trials in Europe and conducted in 49 centers. This randomized, double-blind and placebo-controlled study analyzed data from 212 patients. As was announced by the company last year [4], the study met its primary endpoint: combined remission in intention-to-treat patients was 50% in experimental group versus 34% in placebo group. Tigenix has submitted marketing authorization application to the EMA earlier this year and is expecting approval by the beginning of next 2017.

NK CELL THERAPY TRIAL FOR MYELOID LEUKEMIA SHOWS POSITIVE OUTCOME

Results of aclinical study assessing the safety of a natural killer (NK) cell therapy in patients with acute myeloid leukemia (AML) were published in *Science Translational Medicine* [5]. Even though it was a small safety trial, it is important to note that researchers observed complete remission responses in 4 out of 9 treated patients. This is a fairly high response rate compared to previous NK cell-based clinical trials. The authors attribute this success to their particular approach to culturing the so-called "memory-like NK cells". However, these results must be confirmed in future efficacy studies with larger number of patients for a solid conclusion to be drawn.

CAR-T TRIAL SHOWS PROMISE IN NON-HODGKIN'S LYMPHOMA PATIENTS

Investigators from the Fred Hutchinson Cancer Center, USA, published results from their CAR T-cell therapy trial in 32 patients with non-Hodgkin's lymphoma [6].

The trial used defined compositions of CAR T-cell products, where selected CD4+ and CD8+ cells were cultured separately and mixed 1:1 before administration. Addition of fludarabine to the lymphodepletion regimen before cell therapy administration boosted the complete remission rate from 8 to 50% at 1 month post infusion. Addition of fludarabine to conditioning regimen also led to increase of CAR T-cells persistence *in vivo*. Importantly, no difference in T-cell expansion, *in vivo* persistence

DOI: 10.18609/cgti.2016.046

and clinical responses were observed whether the bulk of CD8+ cells or central memory CD8+ cells were used for manufacturing. The study identified several treatment characteristics that correlated with the therapeutic response and toxicity, including the role of pre-condition regimen used for lymphodepletion before CAR-T cell treatment.

MSC INFUSION AFTER HSCT RENDERS IMMUNE TOLERANCE

Despite availability of some approved stem cell products for the treatment of Graft-versus-Hosts-Disease (GvHD), a severe complication of hematopoietic stem cell transplantation in hematological malignancies, the value of mesenchymal stromal cells (MSC) for prophylactic treatment of chronic GvHD is still unknown. Chinese researchers have recently published results from a multicenter, randomized, double-blind, controlled Phase 2 trial, which assessed the efficacy of allogeneic umbilical cord-derived MSCs for prophylaxis of chronic GvHD in 112 patients [7]. Administration of MSCs after haplo-identical stem cell transplant led to a reduction in the incidence of chronic GvHD by almost half (27.4% in MSC group versus 49% in saline group) at the 2-year mark. The incidence of relapses and overall survival did not differ between the groups. Every patient received 2–4 infusions of 30 million MSCs, starting at 4 months after stem cell transplant. MSC infusions were well tolerated.

CORD BLOOD-DERIVED STEM CELLS HOLD HOPE FOR PATIENTS WITH OSTEOARTHRITIC KNEES

The first stem cell product derived from cord blood MSCs – Cartistem – was approved in South Korea in 2012. Recently, the long-term follow-up study for Cartistem was published [8], in which durability and safety of the product was analyzed for up to 7 years following administration. The authors were able to enrol only seven patients. Unfortunately these patients consented for different follow-up procedures at different time points so there was not a uniform assessment. For example, only two patients consented to undergo arthroscopic examination at 1-year mark, which demonstrated "glossy white hyaline-like cartilage". Importantly, the effects of Cartistem were durable over the 7-year follow up period and there were no cases of tumorigenesis observed over this time.

REFERENCES

1. Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells for Improving Exercise Capacity in Subjects With Refractory Angina (RENEW). Website https://clinicaltrials.gov/show/NCT01508910
2. Povsic TJ, Henry TD, Traverse JH *et al.* The RENEW Trial : Efficacy and Safety of Intramyocardial Autologous CD34+ Cell Administration in Patients With Refractory Angina. *JACC Cardiovasc Interv.* 2016 9(15), 1576–85.
3. Panés J[1], García-Olmo D[2], Van Assche G *et al.* Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. *Lancet.* 2016; pii: S0140-6736(16), 31203-X.
4. Results of Tigenix Phase 3 trial in Crohn's disease fistulas; Press Release. http://stemcellassays.com/2015/08/cells-weekly-august-23-2015/
5. Romee R, Rosario M, Berrien-Elliott MM *et al.* Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. *Sci. Transl. Med.* 2016 8(357), 357ra123.
6. Turtle CJ, Hanafi LA, Berger C *et al.* Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. *Sci. Transl. Med.* 2016 8(355), 355ra116.
7. Gao L, Zhang Y, Hu B *et al.* Phase II Multicenter, Randomized, Double-Blind Controlled Study of Efficacy and Safety of Umbilical Cord-Derived Mesenchymal Stromal Cells in the Prophylaxis of Chronic Graft-Versus-Host Disease After HLA-Haploidentical Stem-Cell Transplantation. *J. Clin. Oncol.* 2016; 34(24), 2843–50.
8. Park YB, Ha CW, Lee CH, Yoon YC, Park YG. Cartilage Regeneration in Osteoarthritic Patients by a Composite of Allogeneic Umbilical Cord Blood-Derived Mesenchymal Stem Cells and Hyaluronate Hydrogel: Results From a Clinical Trial for Safety and Proof-of-Concept With 7 Years of Extended Follow-Up. *Stem Cells Transl. Med.* 2016; pii: sctm.2016-0157.

DOI: 10.18609/cgti.2016.046