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...working for the thalassaemia community

Gene therapy trials begin in the UK

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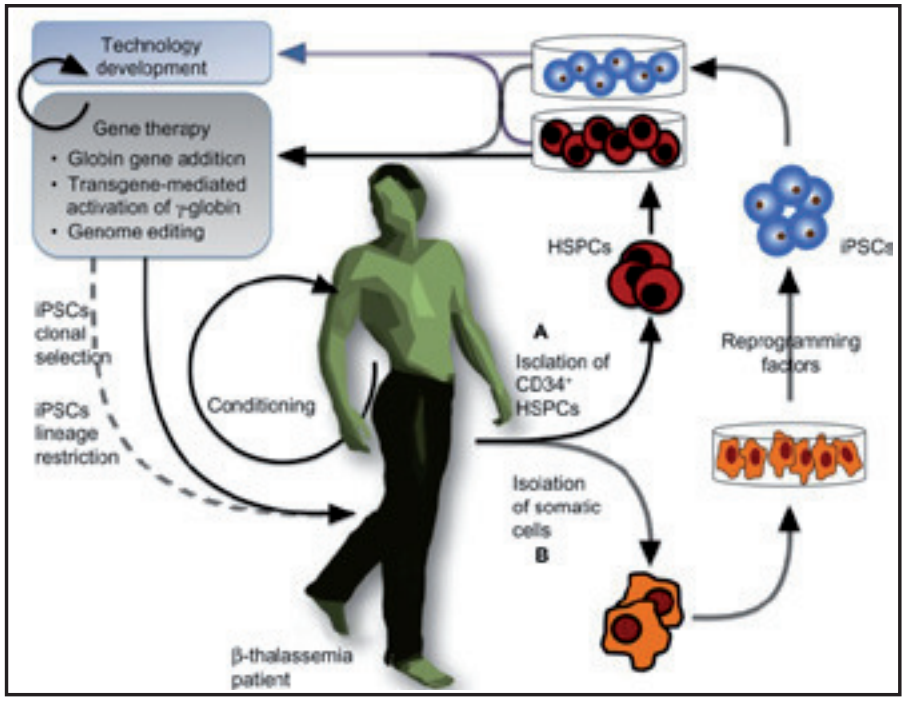

We have finally and thankfully approached the time when gene therapy can be applied to genetic disorders such as thalassaemia. We can now talk with great optimism about the upcoming phase 3 gene therapy clinical trial in transfusion dependent thalassaemia patients. The phase 3 clinical trial is opening imminently and will play a crucial role in determining whether LentiGlobin has the potential to become a standard of care for carefully selected b thalassaemia patients.

As well known, β-thalassemia is caused by mutations reducing or abrogating β-globin expression, which lead to reduced adult haemoglobin and excess α-globin content in red cells, resulting in ineffective erythropoiesis and early red cell destruction. Most β-thalassemia patients therefore require lifelong clinical management by blood transfusion and iron chelation therapy,with a few having the option of curative but potentially hazardous allogeneic stem cell transplantation. Understandably, this procedure is not suitable for every patient and is generally only offered to children with matched sibling donors, who account for around a quarter of all beta thalassaemia cases. This indicates the need for alternative therapies, which if not to cure the disease, then to reduce transfusion requirements and the significant cost of disease management.

Recent progress in the research of disease modifiers,chemical modulation of gene expression and tools and approaches for DNA-based therapies have opened new avenues toward novel and more personalized strategies to manage or cure β-thalassemia.

In the early phase gene therapy trials, patients had haematopoietic stem cells collected from their bone marrow, which were then transfected with an engineered lentivirus carrying a functional copy of

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the gene coding for beta-globin, which is defective in thalassaemia. The cells were then infused back into the patient in the hope they would 'seed' the bone marrow and produce functional red blood cells.

Historically, Lentiviral vectors based on human immunodeficiency virus have been developed for this purpose and had been shown to be effective in curing thalassemia in mouse models. Ongoing efforts have been and are being focused on improving the efficiency of lentiviral vector–mediated gene transfer into stem cells so that the curative potential of gene transfer can be consistently achieved.

The results of the early phase gene therapy trials in thalassaemia, demonstrate the potential for a one-time gene therapy treatment to transform the lives of patients with beta-thalassemia major while avoiding immune complications associated with allogeneic stem cell transplant -indeed a long longed vision.

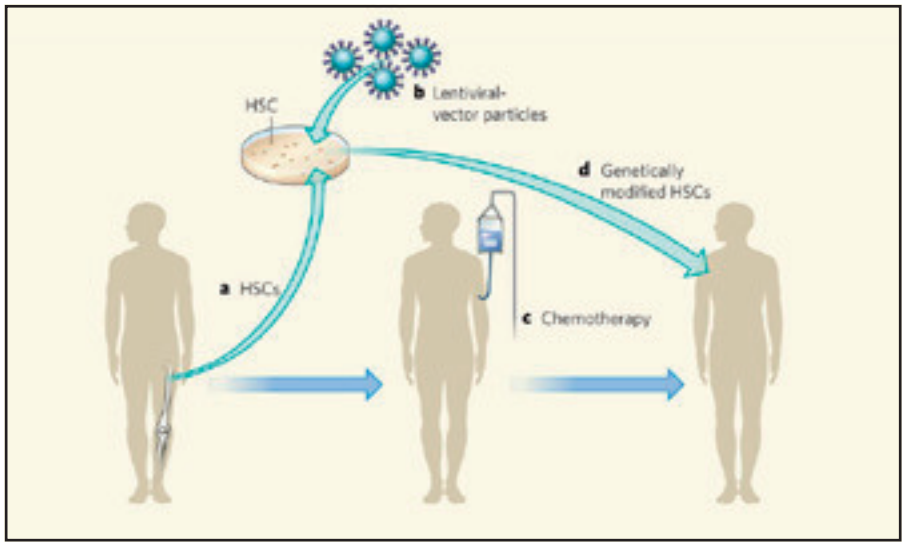
About the early phase gene therapy clinical trials in slightly more detail:

Up until now, 22 patients with thalassaemia and sickle cell disease have had gene therapy within 2 early phase clinical trials run by BluebirdBio.

The Northstar Study is an international, multicenter Phase 1/2 study designed to evaluate the safety in 10 patients with non-β0/β0 genotypes and 8 patients with β0/β0 genotypes who have received LentiGlobin drug product. The median follow-up was 17 months (range: 6.3 – 29.8 months); two patients have completed the two-year primary analysis period.

- All patients with non-β0/β0 geno-types with ≥12 months of follow-up (n=5) have stopped regular transfusions.At last follow-up, the median total hemoglobin of all patients (n=10) with non-β0/ β0 genotypes (median follow up: 14.7 months); was 10.3 g/dL.

- Patients with β0/ β0 genotypes and ≥12 months of follow-up had a median reduction in annualized transfusion volume of 63% and median reduction in annualized transfusion frequency of 65%, calculated based on their transfusion requirements from month 6 to data cut-off. The median follow-up was 17.3 months.



The safety profile remains consistent with myeloablative conditioning using single agent busulfan with no drug product-related adverse events reported.

In the next few weeks we are very excited indeed to welcome a phase 3, multicentre clinical trial by Blue-birdBio, which will open in the UK (UCLH UK site), using an improved manufacturing process that increases transduction efficiency. It is believed that the addition of transduction enhancers to the manufacturing process has the potential to substantially increase the hemoglobin levels in patients with transfusion dependent b-thalassemia and increase their likelihood of achieving clinically meaningful reductions in transfusion requirements or transfusion independence.

The aim of this trial is to evaluate the safety and efficacy of the gene therapy in patients with transfusion dependent b-thalassaemia. The first group of patients studied in this trial will have to have non b0/b0 geno-type but it is hoped that soon the b0/b0 patients will be included in a separate trial. The age group of patients will be 12 and above to 50 or less.The gene therapy will be achieved as in the previous trials, by transplantation of autologous stem cells which were transduced ex vivo (in the laboratory) with the lentiviral b Globin vector. This is an international, multi centre trial and is currently active and enrolling TDT(transfusion dependent thalassaemia) patients in the EU already. The primary efficacy endpoint is the proportion of patients who meet the definition of 'transfusion independence'. This is defined as an average Hb >or equal to 90 g/l without any RBC transfusions, for a continuous period of > or equal to 12 months at any time during the study after drug product infusion. With regard to the way the trial will be conducted: the patients enrolled will first undergo a phase called' mobilisation' whereby stem cells are collected from the blood (apheresis), subsequently they will have to have chemotherapy for 4 consecutive days and finally the stem cells (which had in the meantime been transduced with the b global lentiviral vector) will be re-infused to the patient. As expected, the chemotherapy administered (busulfan), will carry risks of potential complications, such as severe infections, especially whilst the white blood cells remain low. Once the white cell count has recovered and the patient is well, they will be discharged with plans for regular out-patient monitoring the red celland transplant clinics. The follow up within the trial is for 2 years.

We are all (patients and experts) looking forward to following up the progress of the patients who participated in the early phase trials with the particular interest in long term safety. The phase 3 clinical trial is opening imminently and will play a crucial role in the establishment of this curative option as standard of care for carefully selected b thalassaemia patients.