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POSTER ABSTRACTS

801.GENE THERAPIES

Gene Therapy of Transfusion-Dependent β-Thalassemia Patients with Quick Engraftment of Reinfused Hematopoietic Stem Cells: An Investigator-Initiated Trial of KL003

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Introduction

In recent years, autologous hematopoietic stem cell (HSC)-based gene therapy has emerged as one of the most promising curative therapies for the treatment of severe hereditary anemia, including β-thalassemia major. Although several clinical trials of gene therapy for β-thalassemia major patients have been completed in developed countries, clinical data of gene therapy remain scarce for patients in developing countries. These patients are often in poor clinical condition because of severe iron overload and insufficient blood transfusion due to limited blood supply. They account for the majority of the β-thalassemia major patients in developing countries. Unlike in developed countries, most β-thalassemia major patients in developing countries cannot survive to adulthood as a consequence of irregular treatments due to the limitation of medical facilities and/or personal financial conditions.

Methods

We conducted a non-randomized, single-dose, open-label investigator-initiated clinical trial (ChiCTR2200055565) in representative patients in southern China, including those with ferritin above 5000 μg/L. Among the 11 β-thalassemia major patients (aged 6-22) we enrolled, 6 of the patients were in poor clinical conditions (e.g., medium (3000-5000 μg/L ferritin) to severe (>5000 μg/L ferritin) iron overload) due to inconsistent blood transfusions and iron chelation therapy before enrollment (Table). We treated patients using their own HSCs after transduced *ex vivo* with KL003, a lentiviral vector expressing a functional β-globin gene. We then monitored patients closely for safety and evaluated efficacy of KL003, including stem cell engraftment, hematopoietic reconstitution/recovery, and blood transfusion requirement.

Results

Blood transfusion was no longer needed for all 11 patients from median day 14 (range: 10-30 days) after treatment. The longest duration of no blood transfusion has been 18 months. The median engraftment time was 14 days for neutrophils (range: 8-15 days) and 14 days (range: 11-33 days) for platelets. This is a significant improvement compared with much longer engraftment time from previous autologous HSC-based gene therapies in the literature, which were around 4 weeks for neutrophils and 6 weeks for platelets. It is worth noting that the platelet engraftment time (33 days) for patient No. 07, who had a severe iron overload, was much longer than others (Table). This may represent a common challenge for treating patients with severe iron overload.

The safety profile was consistent with that typical of busulfan-based myeloablation conditioning. There were no severe adverse events associated with KL003.

Conclusion

Our clinical trial results demonstrate potentially curative results in β-thalassemia major patients, including those in poor clinical condition. In addition, the optimized transduction process of HSCs may have contributed to maintaining stemness of HSCs, which is essential for quick engraftment and often gets lost during *ex vivo* manipulation. This has led to significantly faster engraftment and better efficacy. Thus, KL003 could be a potential functional cure for β-thalassemia major patients.

Disclosures No relevant conflicts of interest to declare.

Patient No.	Age	Sex	Genotype	Prior Splenectomy	Ferritin at Enrollment (μg/L)	Infuse Dose 10^6/kg	Neutrophil Engraftment (Day)	Platelet Engraftment (Day)	Last Red Cell Transfusion (Day)
01	16	F	β+/β0	N	880	3.8	15	19	30
02	9	M	β+/β0	Y	7200	3.9	10	14	10
03	9	F	β0/β0	N	3800	12	8	11	30
04	6	M	β0/β0	N	1300	24	14	12	12
05	7	M	β+/β0	N	1027	20	10	12	10
06	17	M	β+/β0	N	6913	3.95	14	18	16
07	22	M	β0/β0	N	6283	5.4	14	33	25
08	18	M	β+/β0	N	1297	3.74	15	21	14
09	10	M	β0/β0	N	3036	12.54	14	12	10
10	20	M	β+/β0	N	1006	10.84	13	23	21
11	12	F	β+/β0	N	3290	18.8	13	12	13

Figure 1

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