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BETIBEGLOGENE AUTOTEMCEL GENE THERAPY FOR THE TREATMENT OF TRANSFUSION-DEPENDENT B-THALASSEMIA: UPDATED LONG-TERM EFFICACY AND SAFETY RESULTS

Topic: 25. Gene therapy, cellular immunotherapy and vaccination - Clinical

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Background: Betibeglogene autotemcel (beti-cel) is a one-time ex vivo gene therapy for transfusion-dependent β-thalassemia (TDT) that adds functional copies of a modified *HBB* gene, $\beta^{A\text{-}T87Q}$, into patients' hematopoietic stem cells. Gene therapy with beti-cel corrects the underlying cause of TDT to enable lifelong, stable production of functional adult hemoglobin (Hb) sufficient for transfusion independence (TI) and reduction of ineffective erythropoiesis. A total of 63 patients were treated with beti-cel in 2 completed phase 1/2 (Ph1/2; HGB-204, HGB-205) and 2 ongoing phase 3 (Ph3; HGB-207, HGB-212) studies. After 2 years of follow-up, patients could be enrolled in a 13-year long-term follow-up study (LTF-303; NCT02633943). We report LTF-303 interim results in 44 patients with up to 6.4 years' follow-up.

Aims: Assess long-term safety and efficacy of beti-cel in patients with TDT.

Methods: Autologous CD34+ cells were transduced with BB305 lentiviral vector and infused into patients after single-agent, pharmacokinetic-adjusted, busulfan-based myeloablation. In Ph3 studies, transduction used a refined manufacturing process compared with Ph1/2 studies. LTF-303 assessments include Hb, erythropoiesis, iron, and safety. Data are reported as median (min–max).

Results: As of 30 November 2020, 44 patients had enrolled in LTF-303 (age at enrollment in parent studies: 19.5 [7–35] y; Ph1/2: n=22, Ph3: n=22); follow-up was 45.6 (22.9–76.4) mo.

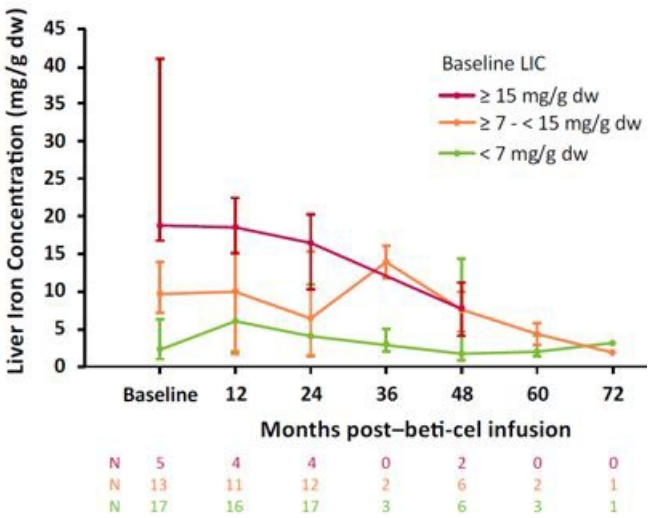
Among patients enrolled in LTF-303, TI (weighted average Hb ≥9 g/dL without packed red blood cell transfusions for ≥12 mo) was achieved and maintained over time in 15/22 (68.2%) patients treated in Ph1/2 and 20/22 (90.9%) patients treated in Ph3. Weighted average Hb during TI was 10.3 and 11.8 g/dL in patients in Ph1/2 and Ph3, respectively. In patients who achieved TI, total Hb over time without transfusion support was maintained from 24 mo (Ph1/2: 10.3 [8.6–13.7] g/dL [n=14]; Ph3: 12.5 [9.7–14.0] g/dL [n=19]) to 36 mo (Ph1/2: 10.5 [8.5–13.5] g/dL [n=15]; Ph3: 12.3 [11.7–13.5] g/dL [n=4]). This was driven by beti-cel–derived HbA^{T87Q} levels and remained stable from 24 mo (Ph1/2: 7.3 [2.9–10.1] g/dL [n=15]; Ph3: 9.4 [5.0–12.4] g/dL [n=19]) to 36 mo (Ph1/2: 7.6 [3.7–10.1] g/dL [n=15]; Ph3: 10.6 [8.6–13.0] g/dL [n=7]). In patients achieving TI in Ph3, soluble transferrin receptor decreased from baseline (129.4 [65.9–235.3] nmol/L, n=20; no patient within normal range) to 24 mo (60.0 [17.7–121.2] nmol/L, n=19; 6 patients within normal range).

Iron removal therapy was managed at the discretion of the investigator and did not target an optimal liver iron concentration (LIC). While the LIC increased just after beti-cel infusion, levels decreased over time in patients who achieved TI, particularly in those who had an elevated LIC at baseline (**Figure**).

No drug product–related AEs were reported >2 years post–beti-cel infusion. Serious AEs occurring after 2 years of follow-up included gonadotropic insufficiency, ectopic pregnancy, fetal death, gallbladder wall thickening/polyp, bacteremia with neutropenia, and major depression (all n=1). No deaths, replication competent lentivirus, or insertional oncogenesis were reported in these patients.

Image:

Figure. Liver iron concentration (LIC) over time by baseline value in patients who achieved transfusion independence and enrolled in LTF-303



Summary/Conclusion: These results demonstrate durability and stability of response after beti-cel gene therapy in patients with TDT with no AEs considered related to beti-cel by the investigator >2 years post-infusion. Sustained levels of HbA^{T87Q} and effective iron reduction improved hematologic parameters and lowered iron burden.

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