Gene Therapy for Sickle Cell Disease, β-Thalassemia Enters Regulatory Reviews

A potential 1-time gene editing treatment for severe sickle cell disease (SCD) and transfusion-dependent β-thalassemia (TDT) is entering approval review by the US Food and Drug Administration (FDA), the European Medicines Agency, and the UK Medicines and Healthcare products Regulatory Agency, according to a company statement.

Both diseases involve variants in the gene encoding β globin. The variants damage β globin in patients with SCD and reduce or eliminate it in patients with TDT. With exagamglogene autotemcel treatment, called exa-cel by developers Vertex Pharmaceuticals and CRISPR Therapeutics, the patient’s own hematopoietic stem cells are harvested and gene edited to produce high levels of fetal hemoglobin (HbF) in red blood cells. The edited cells are then infused back into the patient as part of an autologous hematopoietic stem cell transplant.

The treatment is intended to increase production of HbF, which normally decreases dramatically during infancy. Doing so should raise HbF and total hemoglobin levels, reducing the need for transfusions among patients with TDT and vaso-occlusive episodes among patients with SCD.

Interim results from the first 75 patients in 2 ongoing pivotal trials showed a single dose of exa-cel eliminated the need for red blood cell transfusions among 42 of 44 patients with TDT and reduced them more than 70% among the other 2 patients. Severe vaso-occlusive episodes were eliminated after treatment among 31 patients with SCD. The results were presented at the European Hematology Association Congress in June 2022.

The study participants were followed up from 1.2 months to 37 months after infusion. Among the patients with TDT followed up for more than 3 months, HbF levels eventually increased to about 40% of total hemoglobin. Both groups’ average total hemoglobin levels increased to greater than 11 g/dL for the duration of follow-up. Two patients with TDT had serious treatment-related adverse events.

“By reactivating a naturally occurring developmental process, exa-cel restores fetal hemoglobin production and thereby can ameliorate the course of these diseases,” investigator Haydar Frangoul, MD, medical director of pediatric hematology and oncology at TriStar Centennial Medical Center, said in a company statement.

The European and UK data submissions are expected by the end of this year, while the FDA rolling review submission is targeted for completion in early 2023, the company said.

Noninvasive Neuromodulation May Help Improve Function in Cerebral Palsy

An investigational external neuromodulation device combined with activity-based neurorehabilitation therapy improved gross motor function—including the ability to take independent steps—among children with cerebral palsy in a pilot study reported in Nature Communications. Although the improvements were both clinically and statistically significant, outcomes with neurorehabilitation therapy alone need further assessing, according to the authors.

The spinal neuromodulation device, called SCiP by manufacturer SpineX Inc, attaches to the neck, mid-back, and hips, where it modulates transcutaneous electrical spinal cord signals to the spinal cord and other nerve centers. The authors hypothesize that this enhances neural communication in both directions, increasing neuroplasticity and enabling sensorimotor learning. Such neuromodulation has been shown to aid breathing and functional recovery of the upper and lower extremities, trunk, bladder, and bowel after spinal cord injuries, they wrote.

The study involved 16 children aged 2 years to 16 years with cerebral palsy, 9 of whom were nonambulatory with Gross Motor Function Classification Scale level I-II and 7 of whom were able to take some steps with level I-II. After 8 weeks of twice-weekly combined treatment, all the children showed sensorimotor functional gains. Only 4 children were nonambulatory, 3 were capable of stepping with minimal assistance, and 10 were able to step independently with no external assistance. These improvements corresponded with a 15-point increase on the Gross Motor Function Classification Scale for patients with level I-II and an 11-point increase for patients with level IV-V.

The results suggest that a combined neuromodulation and neurorehabilitation approach may improve self-initiated sensorimotor functions in people with cerebral palsy, the authors concluded.

Bionic Pancreas Outperforms Standard Care for Type 1 Diabetes in Trial

An investigational bionic pancreas that makes insulin dose decisions based on patient body weight and meal announcements without carbohydrate counts did a better job of keeping blood glucose within target ranges than standard care in a recent trial.

The randomized trial involved 326 adults and children with type 1 diabetes. It compared glucose control among 219 patients who received a bionic pancreas with 107 patients who continued their standard care, which included semiautomated insulin delivery systems that require carbohydrate counts and other manual interventions. At screening, 34% of participants used multiple daily insulin injections, 31% used a hybrid closed-loop...
system, 31% used an insulin pump without automation, and 4% used a predictive low-glucose suspension system.

After 13 weeks, the primary end point of mean glycated hemoglobin level decreased from 7.9% to 7.3% in the bionic pancreas group but was unchanged in the standard care group at 7.7%. The mean adjusted between-group difference was −0.5 percentage points.

Mean adjusted glucose level as assessed by continuous glucose monitoring was 16 mg/dL lower in the bionic pancreas group. The percentage of time that the group's glucose level was in the target range of 70 mg/dL to 180 mg/dL was 11 percentage points higher, translating to an additional 2.6 hours per day within the target range. The percentage of time with blood glucose level greater than 170 mg/dL and 250 mg/dL was also lower in the bionic pancreas group, whereas time with a glucose level of less than 70 mg/dL was similar in both groups.

The benefits of the bionic pancreas, called iLet, were more apparent among patients using multiple daily injections than among those using hybrid closed-loop systems.

The bionic pancreas group experienced 17.7 severe hypoglycemic events per 100 participant-years compared with 10.8 severe hypoglycemic events per 100 participant-years in the standard care group. Neither group experienced episodes of diabetic ketoacidosis.

Although death and cardiovascular disease rates have decreased for people with type 1 diabetes, they're still higher than among the general population, according to the accompanying editorial in the

New England Journal of Medicine. “The time is now to close this chasm, and simplified, automated insulin delivery, as with the bionic pancreas, may be the solution,” the editor wrote. — Howard D. Larkin

Note: Source references are available through embedded hyperlinks in the article text online.