First Gene Therapy Approved for Rare Skin Disorder

On May 19, 2023, the FDA approved Vyjuvek™ (beremagene geperpavec), the first gene therapy for the treatment of wounds in patients with dystrophic epidermolysis bullosa (DEB). DEB is a rare genetic disorder that is hallmarked by extremely fragile skin that rips and blisters with even the slightest friction, leading to open wounds that are prone to skin infections and fibrosis. The disease is caused by mutations in the *COL7A1* gene which leads to a deficiency in collagen 7 (COL7), an essential structural protein that helps strengthen and stabilize the outer and middle layers of the skin. When COL7A1 is deficient, skin layers can separate, causing painful and debilitating blisters and wounds. Symptoms are usually present at birth and can vary widely. In mild cases, blistering is primarily found on the hands, feet, knees, and elbows. Patients with more severe disease may experience a variety of serious medical conditions including painful and debilitating widespread blistering that can lead to vision loss and fusion of the fingers and toes. Blisters in the lining of the mouth and digestive tract often result in poor growth and nutrition as well as anemia. With the severe form of DEB, the lifetime risk of developing aggressive skin cancer is higher than 90%. According to the United States National Epidermolysis Bullosa Registry, the incidence and prevalence of dystrophic epidermolysis bullosa is between 1.35 and 3.05 cases per 1 million live births.

Vyjuvek is a non-invasive, topical, redosable gene therapy designed to address the genetic cause of DEB. It uses a modified and harmless version of the herpes simplex virus to deliver two healthy copies of the *COL7A1* gene directly to the skin cells in the wounds. The new gene allows skin cells to produce functional COL7 protein, which increases the skin's structural integrity, helping to reduce blistering and repair wounds. Vyjuvek is available in a biological suspension, which is mixed with a non-active ingredient gel before being applied to the skin. The dosage can be measured in plaque-forming units (PFU, the number of individual virus particles) or in the volume applied (in milliliters). The gel is applied once per week as droplets over the wound, with each droplet spaced about a centimeter apart from other droplets. The therapy may be applied in a healthcare setting or at home, but the application should always be performed by a healthcare professional. The recommended dose depends on the size of the wound. For patients younger than age 3, the maximum weekly dose should not exceed 1.6 billion PFU (0.8 mL). For patients ages 3 and older, the maximum weekly dose is 3.2 billion PFU (1.6 mL). It may not be possible to treat all wounds in a single patient's visit. It is recommended that individual wounds be selected and treated until they are closed before treatment begins on other wounds. If a previously healed wound re-opens, it should be prioritized for treatment.

The FDA approval of Vyjuvek was based on two clinical studies, GEM-1 and GEM-3. The GEM-1 trial tested the safety and efficacy of Vyjuvek in six adults and three children who had a more severe form of DEB. In all participants, one wound was treated with Vyjuvek, while a different wound with a corresponding size was administered a placebo. The wounds that were given placebo showed varying amounts of healing or worsening. In comparison, all but one of the wounds treated with Vyjuvek closed completely and remained healed for at least three months. Complete wound closure was defined as ≥90% reduction from baseline wound surface area. The GEM-3 study enrolled 31 people, most with the more severe form of DEB. As with GEM-1, each participant had one wound treated with Vyjuvek, while another wound was administered the placebo. The results showed that, after three months of treatment, significantly more wounds treated with Vyjuvek than placebo had healed (68% vs. 23%). A similar difference was seen after six months of treatment (65% vs. 26%), meeting the study's main

objective. In both studies, Vyjuvek was generally safe and well tolerated with no reported serious treatment-related adverse events.

Current treatment for DEB has been largely supportive. It includes wound care, control of infection, along with prevention strategies, and treatment of any complications. As a result, many patients suffer from constant pain, discomfort, poor nutrition, and disfigurement. Vyjuvek appears to offer people living with DEB the opportunity for an improved quality of life. Because Vyjuvek works to correct the underlying skin defect of DEB, the therapy appears to not only close existing wounds but also prevent skin from re-blistering and reopening. The durability of the wound closure remains a concern, but to date, data has initially been positive. The new gene therapy is expected to be available in the third quarter of 2023 with an anticipated price of $24,250 per vial. For the average patient this translates to an estimated cost of $631,000 per year. Longer term studies should provide a better understanding of the required length of therapy and possible need for continued retreatment.

Two additional gene therapies are in Phase 3 trials for the treatment of patients with DEB. D-Fi (debcoemagene autoficel) is a personalized cell-based therapy made from the patient's own skin cells. After being collected, the cells are genetically modified in the lab to produce a healthy version of the COL7 protein. The modified cells are then placed via intradermal injection directly into the wounds for at least 2 doses that are given 3 months apart. EB-101 (prademagene zamikeracel) is also manufactured for each patient and provides a corrected and functional COL7A1 gene. The corrected cells are grown as cultures, then surgically transplanted one time as cell "sheets" onto the patient's wounds to enable normal protein expression and skin function. Both therapies have the potential for approval in 2024.

References

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