Long term use of topical beremagene geperpavec (B-VEC) in two patients with dystrophic epidermolysis bullosa

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BACKGROUND

Dystrophic epidermolysis bullosa (DEB) is a rare genetic blistering skin disease caused by mutations in the *COL7A*1 gene. It can be inherited in an autosomal dominant (DDEB) or recessive (RDEB) manner.

This disease is characterized by skin fragility, painful wounds, and various cutaneous and systemic comorbidities. Currently there are no corrective, approved treatments for DEB.

Beremagene geperpavec (B-VEC) is an investigational engineered replication deficient herpes simplex virus type 1 (HSV-1) based vector, which restores type VII collagen (C7) expression to C7 deficient DEB skin.

B-VEC efficacy was demonstrated in a phase 3, double blinded, placebo-controlled intra-patient, randomized trial over a course of 26 weeks[2]. Statistically significant durable healing of wounds of varying sizes and anatomical locations were seen at 3 and 6 months. Weekly B-VEC was well tolerated and is currently under FDA review.

PURPOSE

Here, we present clinical findings from two DEB patients who received long-term treatment with multiple doses of B-VEC. One male DDEB patient **(Figure 1)** who received B-VEC for over two years during the phase 3 and open label extension trial and one male RDEB patient **(Figure 2)** who received B-VEC for over three years, during both the phase 1/2, phase 3 and open label extension trial.

STUDY DESIGN AND METHODS

Both patients were enrolled at Stanford University (Stanford, CA).

The DDEB patient is a 36-year-old male who presents with generalized blistering of the skin since birth. Genetic testing conducted at age 24 confirmed the diagnosis of DDEB. Analysis indicates he is heterozygous for the pathogenic c.7868G>A (p.Gly2623Asp) mutation of the *COL7A1* gene in exon 105 inherited from his father and heterozygous for a variant with unknown significance c.4899G>A at intron 51 inherited from his mother. The patient's mother and father both present with mild blistering. The patient also has a history of intermittent skin infections and squamous cell carcinoma.

The DDEB patient was enrolled in the phase 3 trial in 2020 and continues receiving B-VEC for wounds in the OLE trial. During treatment, the patient experienced occasional wound infections and a fracture of the fifth metacarpal, but no significant adverse events ascribed to the therapy.

The RDEB patient is a 19-year-old male who presents with generalized blistering of the skin since birth. Genetic testing conducted at age 12 confirmed the diagnosis of RDEB. The patient is heterozygous for the pathogenic c.6697dupC (p.G2233RfsX57) mutation of the *COL7A1* gene in exon 84 and heterozygous for the pathogenic c.7462C>T (p.Q2488X) mutation in exon 98. There is no family history of the disease. The patient was diagnosed with iron deficiency anemia at age 11 and receives iron infusions every four weeks. He also has bilateral hand pseudosyndactyly and esophageal stricture.

The RDEB patient enrolled in the phase 1/2 trial in 2018 and received treatment of B-VEC on skin wounds. He continued onto phase 3 and continues to receive B-VEC for wounds in the open-label extension (OLE) trial. No significant adverse events were reported throughout treatment.

B-VEC (5×10^9 PFU/mL) was applied topically onto open wounds on both the patients' skin once a week. Following application, the treated areas are covered using non-adhesive wrap to keep the B-VEC in place.

RESULTS

Continuous wound healing and evidence of systemic improvement are observed in both patients with long-term administration of B-VEC compared to the baseline without significant related adverse events. Safety and efficacy of wound closure is observed for the DDEB patient. The baseline wound remains closed after weekly B-VEC application.

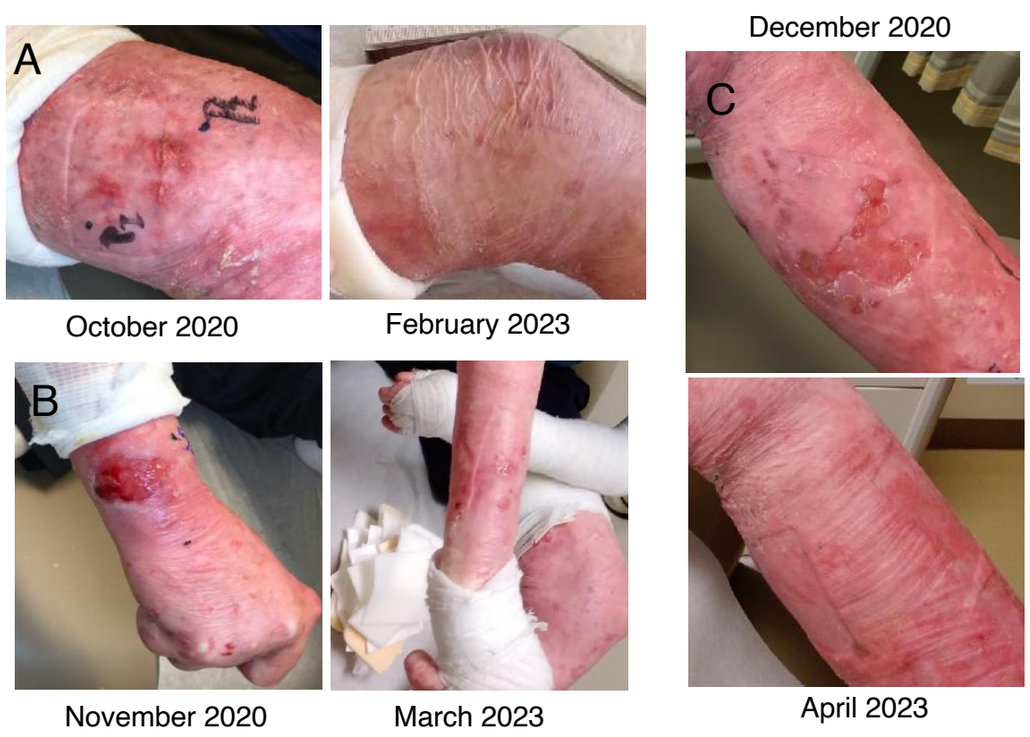

Figure 1: Image of DDEB patient's wound progression. **A:** Left thigh **B:** Right wrist **C:** Left medial shin.

Long-term healing of the RDEB patient's right back is observed from phase 1/2 to the OLE **(Figure 2)**. Along with full closure of the wound, the improvement of the patient's growth and albumin levels **(Figure 3)** were tracked through the study.

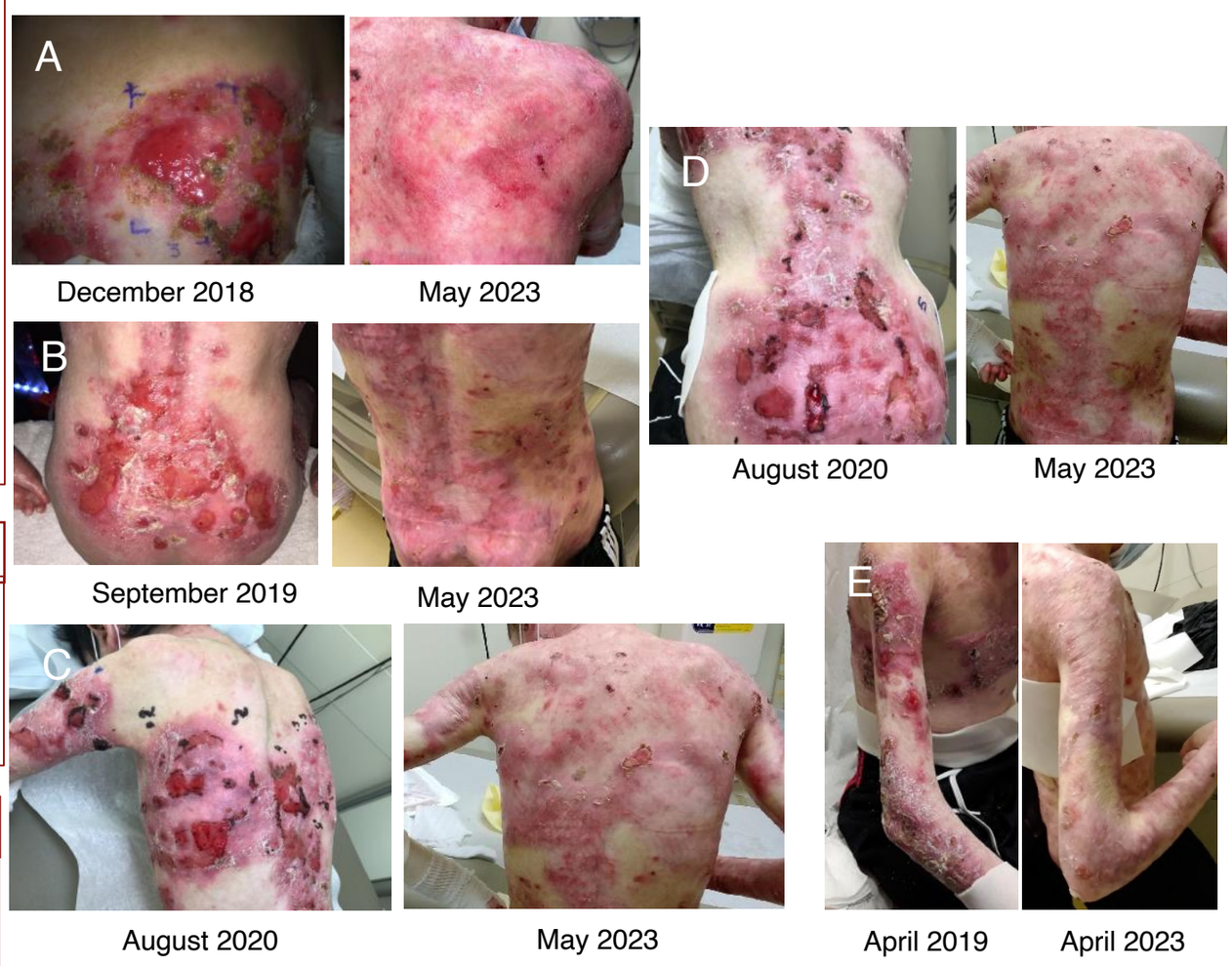

Figure 2: Image of RDEB patient's wound progression. **A:** Right upper back **B:** Lower back **C:** Left upper back **D:** Back (wide angle) **E:** Right upper arm.

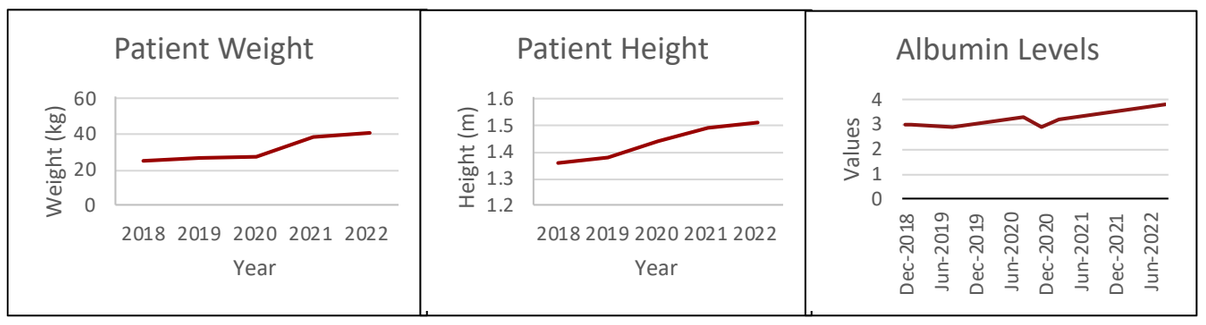

Figure 3: RDEB patient's systemic measures of health are shown through height, weight, and albumin levels.

DISCUSSION

This report demonstrates safety and continued efficacy following long term topical application of B-VEC to DEB skin for **nearly four and a half years**. During this time, wounds remained durably healed, new wounds continued to be responsive to therapy, and there were no significant adverse events attributed to or necessitating pause of long term BVEC therapy.

The RDEB patient started at baseline with widespread and generalized blisters and erosions, however over the course of continued BVEC therapy, his wound burden decreased substantially by 80-90%, and his diagnosis reverted from a severe generalized to an intermediate generalized RDEB phenotype, according to current diagnostic criteria. Over the course of treatment, the RDEB patient demonstrated positive systemic effects of his reduced blistering phenotype and wound burden, including a substantial increase in height and weight as well as in serum albumin.

This report is also the first demonstration of topical gene therapy in a DDEB patient. Like most DDEB patients, this patient showed localized distribution of blistering, however BVEC topical treatment of localized areas of wounding over the course of two and a half years showed a long-term durable healing response without loss of efficacy.

CONCLUSION

In summary, the results add to a growing body of evidence that topical BVEC gene therapy is a convenient, viable, safe, effective and durable long term corrective skin treatment for both RDEB and DDEB patients.

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