Phase I/II open-label trial of intravenous allogeneic mesenchymal stromal cell therapy in adults with recessive dystrophic epidermolysis bullosa

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Background: Recessive dystrophic epidermolysis bullosa (RDEB) is a hereditary blistering disorder due to a lack of type VII collagen. At present, treatment is mainly supportive.

Objectives: To determine whether intravenous allogeneic bone marrow–derived mesenchymal stromal/stem cells (BM-MSCs) are safe in RDEB adults and if the cells improve wound healing and quality of life.

Methods: We conducted a prospective, phase I/II, open-label study recruiting 10 RDEB adults to receive 2 intravenous infusions of BM-MSCs (on day 0 and day 14; each dose 2-4 $\times$ 10^6 cells/kg).

Results: BM-MSCs were well tolerated with no serious adverse events to 12 months. Regarding efficacy, there was a transient reduction in disease activity scores (8/10 subjects) and a significant reduction in itch. One individual showed a transient increase in type VII collagen.

Limitations: Open-label trial with no placebo.

Conclusions: MSC infusion is safe in RDEB adults and can have clinical benefits for at least 2 months. (J Am Acad Dermatol 2020;83:447-54.)

Key words: BM-MSC; epidermolysis bullosa; mesenchymal stromal cells; RDEB.

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Conflicts of interest: None disclosed.

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Epidermolysis bullosa (EB) encompasses a group of rare inherited skin fragility disorders characterized by trauma-induced blistering of the skin and mucous membranes.[1] Biallelic loss-of-function mutations in *COL7A1*, encoding the anchoring fibril protein type VII collagen (C7), result in the recessive dystrophic EB (RDEB) subtypes. In addition to blistering and ulceration from birth, severe forms of RDEB are associated with scarring, contractures, increased risk of squamous cell carcinoma (SCC), systemic inflammation, and symptoms such as itch and pain that collectively have a profound impact on quality of life.[2-4]

Currently there is no cure for RDEB, and management is based on symptom relief, nutritional support, and management of disease complications such as hand contracture release and esophageal dilatation.[5,6] Nonetheless, some progress has been made in the development of new treatments, including gene correction, protein replacement, cell therapy, and pharmacologic approaches.[7,8]

With regard to cell therapy for RDEB, early-phase human clinical trials have been reported using allogeneic fibroblasts (intradermal injections),[9,10] mesenchymal stromal/stem cells (MSCs; intradermal or intravenous),[11,12] and bone marrow (BM) transplantation.[13] MSCs are known to secrete a spectrum of cytokines, chemokines, hormones, growth factors, microvesicles, and exosomes that participate in tissue repair and regeneration, mostly through paracrine actions that mediate cell-to-cell signaling.[14] In vitro, MSCs have also shown a capacity to transport C7 protein and *COL7A1* mRNA to neighboring cells via extracellular vesicles.[15] Moreover, intradermal injections of MSCs can correct RDEB in a xenograft model.[16] However, for allogeneic cells, which are unlikely to persist after administration, it is possible that the MSC secretome is most relevant to enhancing wound healing[17] and potential reduction of fibrosis,[18] although other mechanisms, including MSC apoptosis-induced immunomodulation, may also contribute to clinical benefit.[19]

To date 2 clinical trials of intravenous MSCs in RDEB have been reported.[11,12] In those studies 24 individuals were treated, 23 of whom were children. Both trials reported clinical benefits in terms of better wound healing and symptom improvement that persisted for several months in most individuals. However, the current lack of data in adults with RDEB needs to be addressed. Importantly, the disease biology of RDEB in adults is somewhat different from that in children in that adult RDEB is associated with much greater systemic inflammation, more scarring, and a major increased risk of developing SCC.[2] We have therefore undertaken a phase I/II single-center trial to assess use of intravenous MSCs in adults with RDEB, focusing on safety and early efficacy data and improving understanding of how MSCs may affect disease status and activity.

CAPSULE SUMMARY

- This clinical trial assesses the safety and early efficacy of intravenous mesenchymal stromal cell therapy in adults with recessive dystrophic epidermolysis bullosa for whom current treatment options are limited.
- This form of cell therapy is safe and improves patient symptoms, particularly itch, and reduces skin inflammation and total blister counts.

METHODS

Authorization was granted by the UK Medicines and Healthcare Products Regulatory Agency (EudraCT no. 2014-004500-30). The protocol was approved by the UK National Research Ethics Committee North East—York (REC no. 15/NE/006). After a site-specific agreement, the trial was conducted in accordance with the Declaration of Helsinki principles. The trial was registered with ClinicalTrials.gov (NCT02323789) on December 18, 2014, before the first patient was enrolled on June 12, 2015.

Patient selection

Adults of either sex aged 18 to 65 years with RDEB were invited to take part. The London EB registry (St Thomas' Hospital) was used as the starting point for recruitment and screened against the eligibility criteria for the trial at Guy's and St Thomas' National Health Service Foundation Trust, London. Patients with any malignancy, current or previous, including SCC, were excluded (Fig 1 and Supplemental Table I, available via Mendeley at https://doi.org/10.17632/378kbmxw68.1).

Donor and allogeneic MSCs

Production of BM-MSCs was subject to advanced therapy medicinal product guidelines, and BM-MSCs were manufactured and expanded according to Good Manufacturing Practice regulations. BM-MSCs (not pooled) from 3 healthy unrelated donors were isolated, expanded, cultured, and packaged at the Cell Therapy Facility at University Medical Center Utrecht, Netherlands. The cells were screened against a robust infectious disease panel in accordance with the EU directive 2006/17 (EUD 2006/17/EC). DNA from the donors was screened for *COL7A1* mutations (all negative).

Abbreviations used:

BM:	bone marrow
C7:	type VII collagen
CI:	confidence interval
EB:	epidermolysis bullosa
HMGB-1:	high-mobility group box 1
MSC:	mesenchymal stromal/stem cell
RDEB:	recessive dystrophic epidermolysis bullosa
SCC:	squamous cell carcinoma
SD:	standard deviation
SEM:	standard error of the mean

Clinical procedures

Eight visits were conducted over 8 or 12 months. Monitoring for the occurrence of adverse events was performed at each visit using The Medicine for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 to define adverse events. Each trial participant received 2 separate intravenous infusions of same donor BM-MSCs on day 0 and day 14 (2-4 $\times$ 10^6 cells/kg). Cryopreserved BM-MSCs were thawed and immediately infused via a peripheral cannula. The infusions were given as a day-case procedure; vital signs were checked before MSC administration and at 15, 30, 45, and 60 minutes afterward. The Birmingham Epidermolysis Bullosa Severity Score,[20] Epidermolysis Bullosa Activity and Scarring Index,[21] Quality of Life in EB,[22] and Leuven Itch Scale[23,24] questionnaires were completed to assess clinical responses. Blister counts and clinical photographs were completed by participants during dressing changes, and the data and images were reviewed during each visit. Suction blister induction times were performed at each visit (except on the days of MSC infusion). This measurement was performed on the same site of the same limb using a negative pressure device (Electronic Diversities, Finksburg, MD) (Supplemental Table II, available via Mendeley at https://doi.org/10.17632/378kbmxw68.1).

Laboratory assessments

Blood samples for hematology and biochemistry were taken at all visits. Blood samples were also taken to assess inflammatory markers, and skin biopsies were obtained for immunofluorescence microscopy and transmission electron microscopy (for details see Supplemental Material, available via Mendeley at https://doi.org/10.17632/378kbmxw68.1). To assess gene expression and gene pathways that may be differentially expressed after MSC infusion, RNA and micro-RNA sequencing was performed (for details see Supplemental Material).

RESULTS

Patients

Twelve adults with RDEB were screened against inclusion and exclusion criteria (Supplemental Table I). Of the 12 subjects, 1 was excluded because of the development of SCC during the screening phase and 1 withdrew consent. Ten adults were enrolled in the trial after written informed consent was obtained (Fig 1 and Table I). Adults were recruited between June 2015 and July 2016. All 10 adults received the first infusion of BM-MSCs. The renal profile of 1 patient with known renal impairment showed a deterioration before the first infusion and so was withdrawn; therefore, 9 patients received the second infusion of BM-MSCs. All follow-up visits were completed for all patients in person.

Safety data and adverse events

There were no serious adverse events, and a total of 9 adverse events were experienced by 3 participants (Supplemental Table III, available via Mendeley at https://doi.org/10.17632/378kbmxw68.1). None of the adverse events was related to the BM-MSC infusions, and all adverse events resolved before the end of the study. Two participants (patients 5 and 9) developed SCC during the study period 6 months and 7 months after first MSC infusion, respectively.

Quality of life and clinical severity assessments

Change in clinical features was assessed with photographs (Supplemental Fig 1, available via Mendeley at https://doi.org/10.17632/378kbmxw68.1) and showed little improvement between time points. The mean Birmingham Epidermolysis Bullosa Severity Score decreased slightly at day 28 (0.33; 95% confidence interval [CI], −0.3 to 0.97) and day 60 (1.61; 95% CI, −0.05 to 3.27) when compared with baseline (Supplemental Fig 2, available via Mendeley at https://doi.org/10.17632/378kbmxw68.1). The Quality of Life in EB scale showed a mean reduction in scores at days 28 and 60 of 1.89 (95% CI, −0.87 to 4.65) and 3.13 (95% CI, −0.26 to 6.51) lower than baseline, respectively (Supplemental Fig 2). The Epidermolysis Bullosa Activity and Scarring Index scores overall showed minimal change over time. The activity subscale on average decreased by 4.89 (95% CI, −2.42 to 12.20) and 7.0 (95% CI, −1.59 to 15.59) at days 28 and day 60, respectively, when compared with baseline (Supplemental Fig 2).

Regarding itch, the Leuven Itch Scale is made up of 6 dimensions: frequency, severity, consequences of itch, duration, distress, and body surface area. A reduction in itch frequency was observed at days 28, 60, and 100 and month 6 compared with baseline.

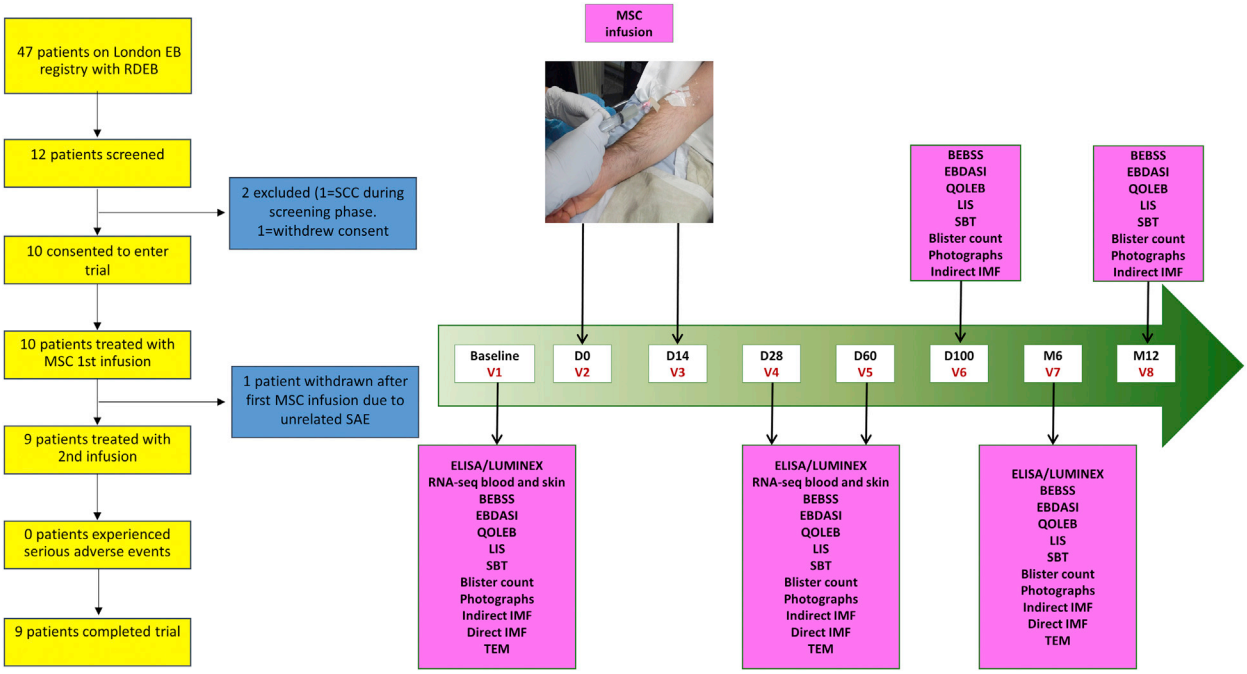

Fig 1. Flowchart for recruitment and trial procedures. *BEBSS*, Birmingham Epidermolysis Bullosa Severity Score; *EB*, epidermolysis bullosa; *EBDASI*, Epidermolysis Bullosa Disease Activity and Scarring Index; *ELISA*, enzyme-linked immunoabsorbent assay; *IMF*, immunofluorescence; *LIS*, Leuven Itch Scale; *MSC*, mesenchymal stromal/stem cell; *QOLEB*, Quality of Life in EB; *RDEB*, recessive dystrophic epidermolysis bullosa; *SAE*, serious adverse event; SBT, suction blister time; *SCC*, squamous cell carcinoma; *TEM*, transmission electron microscopy.

The mean reduction at these times, respectively, was 13.89 (95% CI, 3.76-24.02), 18.75 (95% CI, 9.07-28.43), 15.63 (95% CI, 4.81-26.44), and 12.50 (95% CI, 1.33-23.67). Itch severity scores also showed a decrease, with a mean difference of 15.44 (95% CI, 4.47-26.42) at day 28 and 15.16 (95% CI, −1.74 to 32.05) at day 60 compared with baseline. At day 100 and month 6 the severity of itch returned to levels similar to baseline. Consequences of itch similarly decreased, and the mean difference from baseline was 12.64 (95% CI, 0.40-24.88), 17.21 (95% CI, 6.40-28.01), 14.26 (95% CI, 4.51-24.0), and 10.95 (95% CI, 0.78-21.12) at days 28, 60, and 100 and month 6, respectively. Duration of itch, distress, and body surface area stayed relatively static between time points (Supplemental Fig 3, available via Mendeley at https://doi.org/10.17632/378kbmxw68.1).

Total blister count over the entire body surface area showed a decrease on average at days 28 and 60 compared with baseline. The average decrease was 2.78 (95% CI, −1.67 to 7.22) at day 28 and 2.88 (95% CI, −2.01 to 7.76) at day 60 (Fig 2). Suction blister time on average was slightly longer at day 28 compared with baseline, with an average difference of 10.11 seconds (95% CI, −164.40 to 184.63). Wide variations across patients and within patients were observed. The median suction time was lowest at day 14, highest at day 28, and moderate fluctuation was observed thereafter (Fig 2).

Direct immunofluorescence and ultrastructural microscopy assessment

Of the 9 patients that completed the trial, at baseline 4 individuals had linear and bright C7 expression, similar to control skin, and 5 patients had partial reduction or complete absence of C7 expression (Table I). One patient (patient 6) showed a slight transient increase in C7 expression at the dermal−epidermal junction at days 28 and 60 when compared with baseline; this was associated with an increase in the patient's own (mutant) *COL7A1* mRNA (Supplemental Fig 4, available via Mendeley at https://doi.org/10.17632/378kbmxw68.1) but no new anchoring fibrils. C7 expression in all other participants showed no change (Supplemental Fig 5, available via Mendeley at https://doi.org/10.17632/378kbmxw68.1). Mean fluorescence intensity for C7 immunoreactivity in patient 6 measured 5.44 (standard deviation [SD], 2.55; standard error of the

Table I. Recessive dystrophic epidermolysis bullosa

Characteristic	Patient identification no.									
	2	4	5	6	7	8	9	10	11	12
Age, y	29	31	35	44	26	55	43	27	35	36
Sex	F	F	F	M	M	M	F	F	M	M
COL7A1 mutation	c.2044C>T, p.Arg682*, exon 15; IVS87+4A>G	c.1732C>T, p.Arg578*, exon 13; c.7786delG, p.Gly2596Valfs*3, exon 104	c.1732C>T, p.Arg578* exon 13; c.7474C>T; p.Arg2492* exon 98	c.1732C>T; p.Arg578*, exon 13; IVS20+2T>C	c.186delG; p.Gly62fs*39, exon 2; IVS79+1G>C	c.5047C>T, p.Arg1683*, exon 54; c.5720_5722GA>AT, p.Gly1907Asp, exon 68	c.6637G>A, p.Gly2213Arg, exon 83; c.8372G>C, p.Arg2791Pro exon 113	c.6205C>T, p.Arg2069Cys, exon 74; c.5662insG, p.Pro1888 Alafs*27	c.5047C>T, p.Arg1683*, exon 54; c.5869C>T, p.Arg1957Trp, exon 71	c.6205C>T, p.Arg2069Cys, exon 74; c.6205C>T, p.Arg2069Cys, exon 74
Collagen 7 expression at dermal–epidermal junction	Moderate reduction	Complete absence	Complete absence	Slight reduction	Complete absence	Linear and bright	Linear and bright	Slight reduction	Linear and bright	Linear and bright
Type VII collagen enzyme-linked immunosorbent assay	11	3	7	5	4	3	1	22	1	2
Indirect immunofluorescence microscopy	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Clinical features	Extensive; pseudo syndactyly with widespread erosions trunk and limbs; renal impairment	Extensive; partial pseudo syndactyly with erosions hands feet chest	Extensive; pseudo syndactyly with erosions scalp, trunk, limbs	Extensive; partial pseudo syndactyly with large chronic erosion back; erosions limbs	Extensive; pseudo syndactyly large chronic erosion scalp, chest, back, limbs	Inversa; flexural erosions mainly groin, axillary and perianal; hypertension	Erosions localized to lower legs, mild axillary and submammary involvement	Inversa; flexural erosions axillae, submammary, groin	Inversa; esophageal involvement with mild erosions limbs	Inversa; erosions limited to perianal skin

Clinical demographics of patients recruited to the trial and their *COL7A1* mutations.

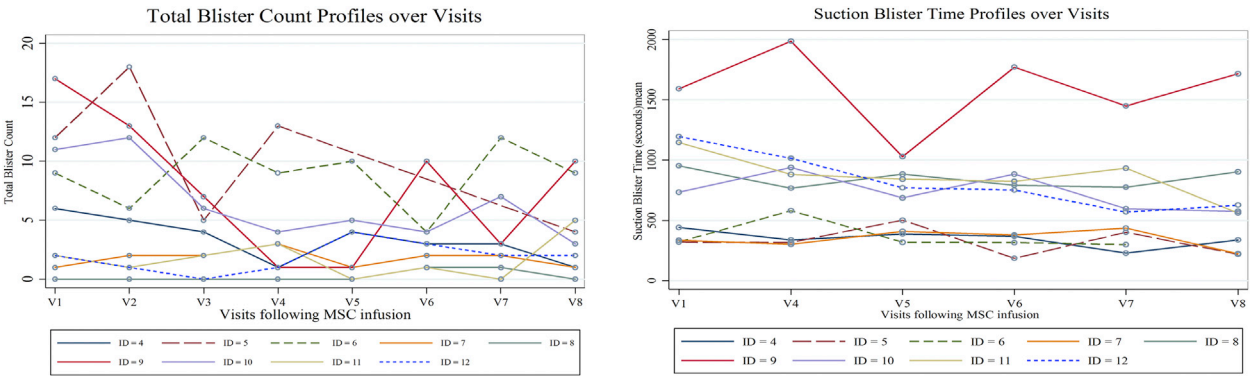

Fig 2. Recessive dystrophic epidermolysis bullosa. Changes in each participant's blister counts and suction blister time across trial visits. *MSC*, Mesenchymal stromal/stem cell.

mean [SEM], ±0.76) at baseline, increased to 8.22 (SD, 3.13; SEM, ±0.74) at day 28, and measured 9.43 (SD, 4.58; SEM, ±1.27) at day 60 (Supplemental Table IV, available via Mendeley at https://doi.org/10.17632/378kbmxw68.1); mean fluorescence intensity measurements for other participants are also included in Supplemental Table IV. Overall, no patient had numeric or morphologic changes in anchoring fibrils at the dermal–epidermal junction after receiving MSCs.

Laboratory results

General inflammatory markers including C-reactive protein and erythrocyte sedimentation rate showed no clear changes over time in any participant (Fig 3). However, high mobility group box-1 (HMGB-1) was lower at days 28 and 60 than at baseline. The mean reduction between baseline and day 28 was 4.86 ng/mL (95% CI, 0.36-9.35) and between baseline and day 60 was 7.19 (95% CI, 1.26-13.11); this biomarker remained low at month 6 when the last measurement was taken (Fig 3). Hemoglobin, white blood cell count, albumin, and creatinine remained similar over time before and after MSC infusion. Mean tumor necrosis factor-α, interferon-γ, interleukin-17A, interleukin-1, interleukin-10, matrix metallopeptidase-2, matrix metallopeptidase-9, matrix metallopeptidase-11 and tissue inhibitor of metalloproteinase-1 showed little change and great variability across patients (data not shown).

DISCUSSION

This trial explored the clinical use of intravenous allogeneic BM-MSCs in 10 adults with RDEB, albeit with the limitation that this was an open-label trial conducted at a single center with no placebo arm. Although the primary objective was safety, we also noted variable and transient improvements, maximal around days 28 and 60 postinfusion of MSCs, particularly in the reduction of pruritus. The activity subscale of the Epidermolysis Bullosa Activity and Scarring Index also showed improvement as did quality of life, as indicated by a reduction in the Quality of Life in EB score, particularly at days 28 and 60. Total blister count showed a decrease in 7 of 9 subjects, with an increase in the median suction blister time that was highest at day 28. These observations might be explained by the reduction in itch, leading to less scratching and skin trauma. In addition, although there was no increase in C7 or anchoring fibrils at the dermal–epidermal junction, we noted increased expression of other junctional adhesion proteins in skin post-MSCs that might account, in part, for improved skin integrity. Infusion of MSCs may also reduce inflammatory mediators that indirectly contribute to dermal–epidermal junction adhesion. Notably, although the serum inflammatory markers C-reactive protein and erythrocyte sedimentation rate showed no clear change over time in any participant, measurement of HMGB-1 was mostly lower at days 28 and 60 after the MSC infusion when compared with baseline. HMGB-1, also known as amphoterin, is a mediator of inflammation[25] that is released from necrotic keratinocytes and is known to be elevated in adults with RDEB.[26] HMGB-1 is also known to mobilize a subpopulation of autologous MSCs to initiate tissue repair.[27] Measurement of HMGB-1 may be worthy of further study as an inflammatory biomarker in other cell therapy trials in adults with RDEB.

As previously reported by Petrof et al,[11] in children with RDEB the MSCs were well tolerated with only mild adverse effects that were mostly transient, all of which were unrelated to the MSCs (Supplemental Table III). One new potential

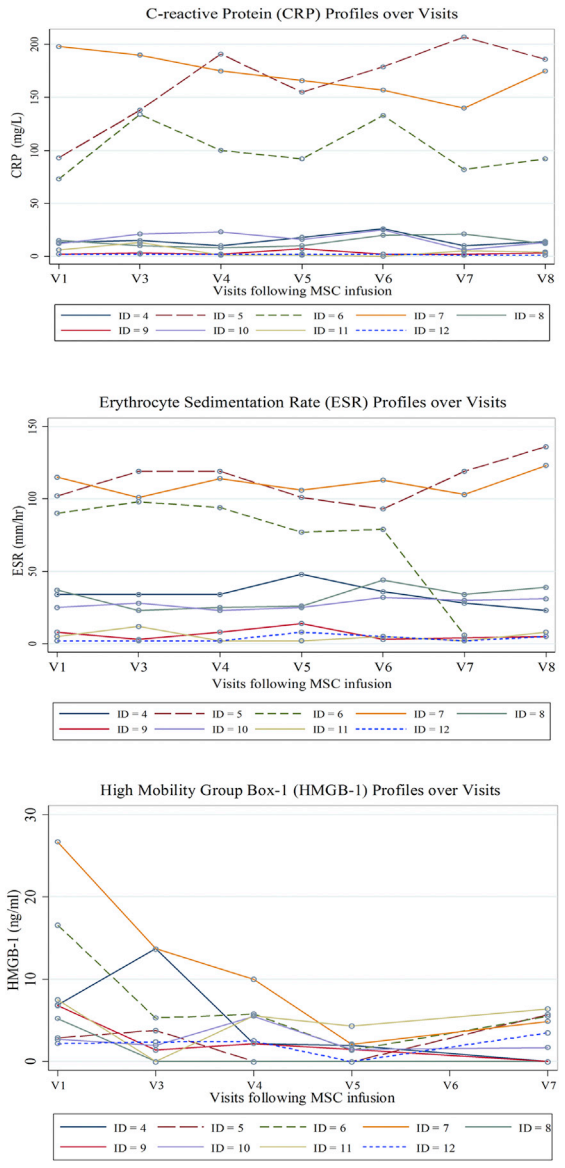

Fig 3. Recessive dystrophic epidermolysis bullosa. Changes in each participant's C-reactive protein, erythrocyte sedimentation rate, and high mobility group box-1 levels across 8 trial visits. *MSC*, Mesenchymal stromal/stem cell.

concern, however, was that 2 participants developed SCC during the study period (patients 5 and 9 at 6 and 7 months after MSCs, respectively). Although individuals with RDEB have a greatly increased inherent risk of developing SCC,[28,29] a key question must be whether the infusion of MSCs might have caused or accelerated the occurrence of SCC. Thus far, more than 700 clinical trials have been performed using MSCs from various sources and for a variety of diseases. Malignancy has not been an evident concern in any of these trials, although recent in vitro and animal model data have shown that MSC exosomes can promote breast cancer cell proliferation and migration via Hippo signaling[30]; no abnormalities in Hippo signaling, however, were evident in our RNA-seq data (see Supplemental Material).

Leuven Itch Scale subscales of frequency, severity, and consequences of itch showed the most changes with a significant reduction at days 28 and 60 after MSC infusion. The mechanism underpinning the improvement in pruritus is not clear. However, after MSC infusion we noted an upregulation of *TRPM6* (RNA-seq blood data). *TRPM6* encodes transient receptor potential cation channel subfamily M member 6, a key regulator of cellular magnesium homeostasis[31,32] and relevant to pruritus.[33] From the patients' perspective, the improvement in itch after MSC infusion was a major health benefit, as noted previously in the pediatric population.[11] In contrast to pediatric studies, however, photographic documentation of wounds before and after MSCs showed highly variable responses, including no change or enlargement of individual wounds (Supplemental Fig 1).

Overall, the use of intravenous MSCs in adults with RDEB appears to be safe, but with the caveat that other similar clinical trials should carefully monitor the potential complication of promoting SCC development or progression. Clinically, although optimal dosing of allogeneic cells is not known, the infusion of 2 doses of MSCs (2-4 $\times$ 10^6 cells/kg) given 14 days apart does have some therapeutic benefit, particularly in reducing itch. Future studies that look to optimize the number and frequency of cell infusions or to address specific subpopulations of MSCs or look to a better understanding of the MSC secretome and the particular role of its components in regenerative medicine[14] are likely to enhance the clinical benefit of cell therapy in RDEB until more disease-specific corrective therapies become available.

REFERENCES

1. Fine JD, Bruckner-Tuderman L, Eady RA, et al. Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. *J Am Acad Dermatol*. 2014;70:1103-1126.
2. Fine JD, Mellerio JE. Extracutaneous manifestations and complications of inherited epidermolysis bullosa: part I. Epithelial associated tissues. *J Am Acad Dermatol*. 2009;61:367-384. quiz 85-6.
3. Jeon IK, On HR, Kim SC. Quality of life and economic burden in recessive dystrophic epidermolysis bullosa. *Ann Dermatol*. 2016;28:6-14.
4. Mellerio JE, Robertson SJ, Bernardis C, et al. Management of cutaneous squamous cell carcinoma in patients with epidermolysis bullosa: best clinical practice guidelines. *Br J Dermatol*. 2016;174:56-67.
5. Mellerio JE, Weiner M, Denyer JE, et al. Medical management of epidermolysis bullosa: proceedings of the IInd International

Symposium on Epidermolysis Bullosa, Santiago, Chile, 2005. *Int J Dermatol*. 2007;46:795-800.
6. Azizkhan RG, Denyer JE, Mellerio JE, et al. Surgical management of epidermolysis bullosa: proceedings of the IInd International Symposium on Epidermolysis Bullosa, Santiago, Chile, 2005. *Int J Dermatol*. 2007;46:801-808.
7. Hsu CK, Wang SP, Lee JY, McGrath JA. Treatment of hereditary epidermolysis bullosa: updates and future prospects. *Am J Clin Dermatol*. 2014;15:1-6.
8. Uitto J, Bruckner-Tuderman L, McGrath JA, Riedl R, Robinson C. Progress in epidermolysis bullosa research toward treatment and cure. *J Invest Dermatol*. 2018;138:1010-1016.
9. Venugopal SS, Yan W, Frew JW, et al. A phase II randomized vehicle-controlled trial of intradermal allogeneic fibroblasts for recessive dystrophic epidermolysis bullosa. *J Am Acad Dermatol*. 2013;69:898-908.
10. Petrof G, Martinez-Queipo M, Mellerio JE, Kemp P, McGrath JA. Fibroblast cell therapy enhances initial healing in recessive dystrophic epidermolysis bullosa wounds: results of a randomized, vehicle-controlled trial. *Br J Dermatol*. 2013;169:1025-1033.
11. Petrof G, Lwin SM, Martinez-Queipo M, et al. Potential of systemic allogeneic mesenchymal stromal cell therapy for children with recessive dystrophic epidermolysis bullosa. *J Invest Dermatol*. 2015;135:2319-2321.
12. El-Darouti M, Fawzy M, Amin I, et al. Treatment of dystrophic epidermolysis bullosa with bone marrow non-hematopoeitic stem cells: a randomized controlled trial. *Dermatol Ther*. 2016;29:96-100.
13. Wagner JE, Ishida-Yamamoto A, McGrath JA, et al. Bone marrow transplantation for recessive dystrophic epidermolysis bullosa. *N Engl J Med*. 2010;363:629-639.
14. Kumar PL, Kandoi S, Misra R, Vijayalakshmi S, Rajagopal K, Verma RS. The mesenchymal stem cell secretome: a new paradigm towards cell-free therapeutic mode in regenerative medicine. *Cytokine Growth Factor Rev*. 2019;46:1-9.
15. McBride JD, Rodriguez-Menocal L, Candanedo A, Guzman W, Garcia-Contreras M, Badiavas EV. Dual mechanism of type VII collagen transfer by bone marrow mesenchymal stem cell extracellular vesicles to recessive dystrophic epidermolysis bullosa fibroblasts. *Biochimie*. 2018;155:50-58.
16. Ganier C, Titeux M, Gaucher S, et al. Intradermal injection of bone marrow mesenchymal stromal cells corrects recessive dystrophic epidermolysis bullosa in a xenograft model. *J Invest Dermatol*. 2018;138:2483-2486.
17. Kosaric N, Kiwanuka H, Gurtner GC. Stem cell therapies for wound healing. *Expert Opin Biol Ther*. 2019;19(6):575-585.
18. An SY, Jang YJ, Lim HJ, et al. Milk fat globule-EGF factor 8, secreted by mesenchymal stem cells, protects against liver fibrosis in mice. *Gastroenterology*. 2017;152:1174-1186.
19. Galleu A, Riffo-Vasquez Y, Trento C, et al. Apoptosis in mesenchymal stromal cells induces in vivo recipient-mediated immunomodulation. *Sci Transl Med*. 2017;9. pii: eaam7828.
20. Moss C, Wong A, Davies P. The Birmingham Epidermolysis Bullosa Severity score: development and validation. *Br J Dermatol*. 2009;160:1057-1065.
21. Loh CC, Kim J, Su JC, et al. Development, reliability, and validity of a novel Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI). *J Am Acad Dermatol*. 2014;70:89-97.e1-13.
22. Frew JW, Martin LK, Nijsten T, Murrell DF. Quality of life evaluation in epidermolysis bullosa (EB) through the development of the QOLEB questionnaire: an EB-specific quality of life instrument. *Br J Dermatol*. 2009;161:1323-1330.
23. Haest C, Casaer MP, Daems A, et al. Measurement of itching: validation of the Leuven Itch Scale. *Burns*. 2011;37:939-950.
24. Snauwaert JJ, Yuen WY, Jonkman MF, Moons P, Naulaers G, Morren MA. Burden of itch in epidermolysis bullosa. *Br J Dermatol*. 2014;171:73-78.
25. Wang H, Bloom O, Zhang M, et al. HMG-1 as a late mediator of endotoxin lethality in mice. *Science*. 1999;285:248-251.
26. Petrof G, Abdul-Wahab A, Proudfoot L, Pramanik R, Mellerio JE, McGrath JA. Serum levels of high mobility group box 1 correlate with disease severity in recessive dystrophic epidermolysis bullosa. *Exp Dermatol*. 2013;22:433-435.
27. Tamai K, Yamazaki T, Chino T, et al. PDGFRalpha-positive cells in bone marrow are mobilized by high mobility group box 1 (HMGB1) to regenerate injured epithelia. *Proc Natl Acad Sci USA*. 2011;108:6609-6614.
28. Rodeck U, Uitto J. Recessive dystrophic epidermolysis bullosa-associated squamous-cell carcinoma: an enigmatic entity with complex pathogenesis. *J Invest Dermatol*. 2007;127:2295-2296.
29. Fine JD, Johnson LB, Weiner M, Li KP, Suchindran C. Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986-2006. *J Am Acad Dermatol*. 2009;60:203-211.
30. Wang S, Su X, Xu M, et al. Exosomes secreted by mesenchymal stromal/stem cell-derived adipocytes promote breast cancer cell growth via activation of Hippo signaling pathway. *Stem Cell Res Ther*. 2019;10:117.
31. Clapham DE. TRP channels as cellular sensors. *Nature*. 2003;426:517-524.
32. Nilius B, Mahieu F. A road map for TR(I)Ps. *Mol Cell*. 2006;22:297-307.
33. Thomsen JS, Nielsen PL, Serup J. The hypomagnesic rat model: dermatitis-prone hairless rats with mild magnesium depletion fed a diet low in lipids did not develop pruritic dermatitis. *Skin Res Technol*. 2005;11:42-46.