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Conflicts of interest

WC has no disclosures on file. PL has served as an investigator for Merck. AMM is an employee of Sun Pharmaceutical Industries, Inc.; and has individual shares in Johnson and Johnson, and as part of retirement account/mutual funds. SJR is an employee of Sun Pharmaceutical Industries, Inc. WL has conducted research funded by AbbVie, Amgen, Janssen, Leo, Novartis, Pfizer, Regeneron/Sanofi and TRex Bio.

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Intravenous allogeneic multilineage-differentiating stress-enduring cells in adults with dystrophic epidermolysis bullosa: a phase 1/2 open-label study

To the Editor,

Epidermolysis bullosa (EB) is a group of genodermatoses characterized by generalized blisters from mutations in the genes encoding the basement membrane zone (BMZ) proteins.[1] The

Table 1 The details of the participants

Patient	1	2	3	4	5
Age, sex	26, F	22, F	20, F	17, M	49, F
Diagnosis	Intermediate RDEB	Intermediate RDEB	Intermediate DDEB	Localized DDEB (pretibial)	Intermediate DDEB
Bodyweight (kg)	42.3	46.2	52.4	75.9	46.0
Number of selected ulcers	2	4	3	2	2
Average ulcer size	1.50	16.00	1.93	8.10	2.20
(cm^2, min–max)	(0.7–2.3)	(1.6–49.2)	(0.9–3.8)	(2.7–13.5)	(1.2–3.2)
Dose of CL2020 ($\times 10^5$ cells/kg)	3.55	3.25	2.86	1.98	3.26
Average reduction rate at Wk04 (%)	100	59.5	37.9	43.2	−9.1

DDEB, dominant dystrophic epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa.

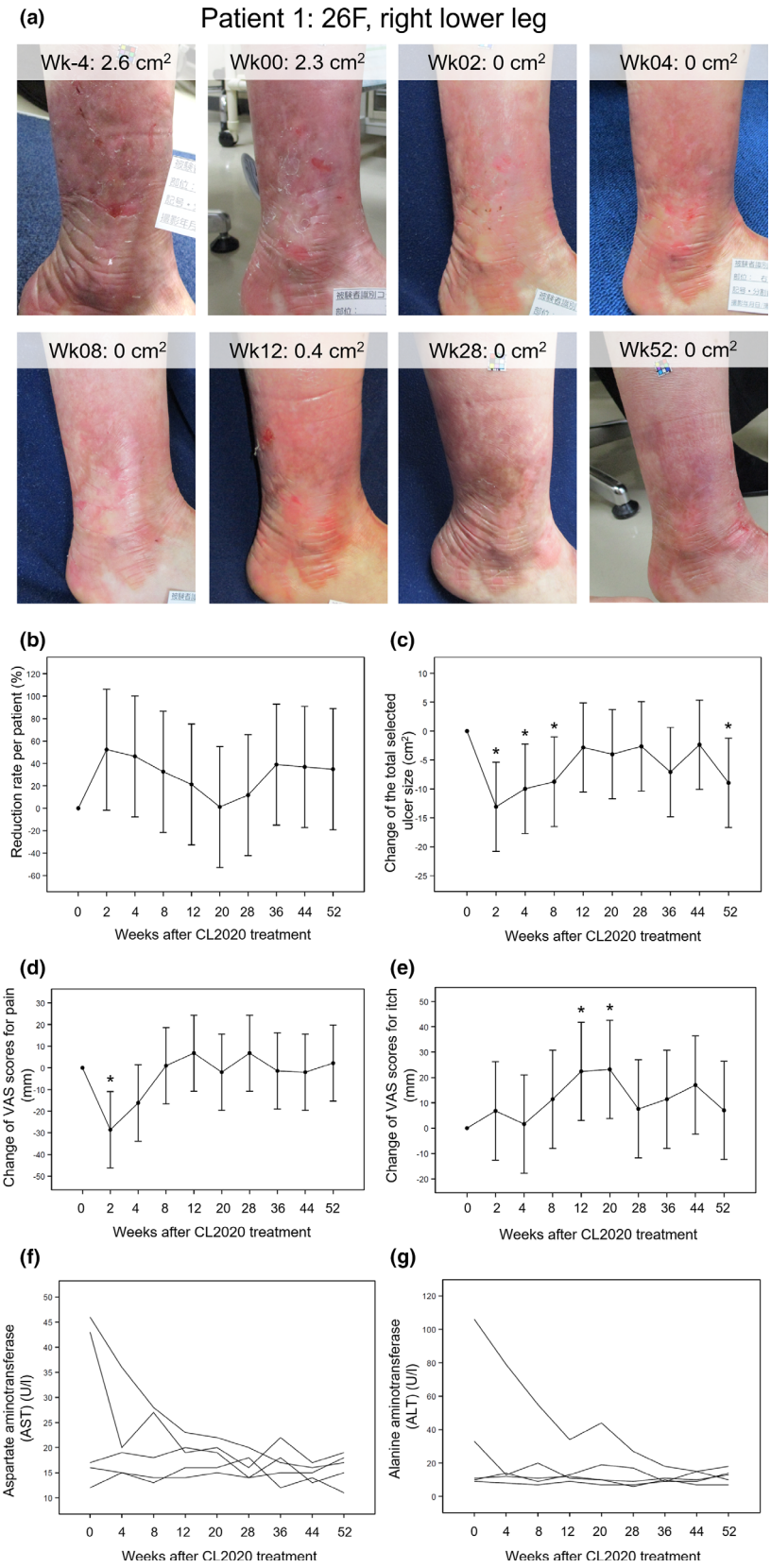

Figure 1 (a) Representative clinical images of the patient (Patient 1, right lower leg). During the observation period from Wk-4 to Wk00, the area of skin erosion was largely unchanged. After CL2020 administration, the area of the erosion rapidly improved. (b) The time course for the reduction rate of ulcer area per patient. Summary statistics (mean and standard deviation) and two-sided 95% confidence intervals for the mean were calculated, and a transition chart was prepared for each subject. Adjusted mean changes from the baseline (95% confidence intervals) were determined using a linear mixed-effects model for all efficacy outcomes. (c) Change in the combined size of selected ulcers from the baseline (cm^2) per patient. (d) Change in visual analogue score (VAS) for pain. At Wk02, a significant reduction is observed. (e) VAS for itch. Itch score increases are noted at Wk12 and Wk20. (f, g) Regarding blood examinations, improvement of liver enzymes is noted in two patients. It may be explained by the tissue regeneration of Muse cells in the liver or the anti-inflammatory effects of Muse cells. Bars: standard deviation. $^*P < 0.05$.

infusion of allogeneic cells such as mesenchymal stem/stromal cells (MSCs), which have intact BMZ genes, is a promising treatment.[2–6] We here focus on multilineage-differentiating stress-enduring (Muse) cells, which were initially found as a stem cell marker stage-specific embryonic antigen (SSEA)-3-positive subpopulation of bone marrow-derived MSCs.[7] Papers have demonstrated that SSEA-3(+) Muse cells have higher pluripotency than the SSEA-3(−) population of MSCs, which suggests that Muse cells are preferable to bulk MSCs for regenerative medicine.[7,8] Very recently, CL2020, a clinical-grade Muse cell product (Life Science Institute, Inc., Tokyo, Japan), demonstrated safety and efficacy in human patients with acute myocardial infarction.[8] In addition, we reported that human Muse cells can differentiate into epidermal keratinocytes with the expression of human BMZ proteins *in vivo*.[9] We herein conducted a pilot study on CL2020 for the treatment of EB in human adults.

This study was designed as an open-label, non-randomized, single-arm, non-controlled clinical trial (JapicCTI-184563). In brief, EB patients with refractory ulcers and recurrent ulcers lasting for more than 4 weeks were selected, measured and followed for 52 weeks after a single infusion of CL2020 containing 1.5×10^7 cells ($2.98 \pm 0.61 \times 10^5$ cells/kg). The reduction rate of the selected skin ulcers per patient (%) was calculated as follows:[10]

$$= \frac{\sum_{\text{lesion}=1}^{n}(\text{Baseline ulcer area}(\text{cm}^2) - \text{Ulcer area at evaluation}(\text{cm}^2))}{\sum_{\text{lesion}=1}^{n}(\text{Baseline ulcer area}(\text{cm}^2))} \times 100.$$

Five patients [one male and four female, ages 17–49 (median: 22)] with 13 ulcers from two institutes were finally enrolled and followed (Table 1). All cases showed mild or self-limiting adverse effects, and the following were reported: stomach pain (Grade 3), acquired lacrimal stricture (G2), fever (G1), gastroenteritis (G1), upper respiratory tract infection (G1) and paraesthesia of the upper arms (G1). One patient showed paraesthesia within 24 h after infusion and resolved in 14 days, which was considered a possible CL2020-related side-effect. Two patients showed a >50% ulcer reduction rate per patient at 4 weeks after CL2020 administration (Wk04, Fig. 1a,b). The average reduction rate at Wk04 was 46.32 [95% confidence interval (CI): −13.59 to 106.22]%. A tendency for the ulcers to improve was observed from Wk02 to Wk08, but overall, the ulcer size returned to the baseline at Wk12. The change in the total size of the selected ulcers was −9.98 (95% CI: −17.87 to −2.09) cm^2 at Wk04, and statistically significant improvement was found ($P = 0.017$, Fig. 1c). Regarding scores for pain, itch and quality of life, only the pain score seems to have improved, and it did so moderately at the early phase ($P = 0.003$ at Wk02, Fig. 1d,e). Blood examinations revealed that liver dysfunction, probably due to chronic inflammation, improved after the CL2020 infusion in two patients (Fig. 1f,g).

We obtained a skin sample at Wk04 from 1 recessive DEB patient and performed immunofluorescence analysis and electron microscopic investigation.[10] No increases in type VII collagen fluorescence intensity or in anchoring fibrils were observed (data not shown).

The limitations of the current study are given here. (i) The single administration of a rather small number of cells might have resulted in the limited clinical efficacy. (ii) Ulcers of somewhat small sizes tended to be included, and three of the five enrolled patients had dominant DEB, which could have adversely affected the endpoint results by frequent scratching. (iii) Only one biopsy was conducted in the trial. (iv) No interventions were performed on children. CL2020 administration is a well-tolerated therapy and Muse cells are a potentially promising regenerative medicine for adults with severe EB.

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The patients in this manuscript have given written informed consent to publication of their case details.

Author contributions

YF conceptualized the study. YF, TN, ST, KN and AI performed data curation. YF and OW performed formal analysis. HS obtained funding. YF, ST, KN and HN investigated the study. YF, ST, KN, SS, TT, MA, AI and HS designed methodology. YF, MA, AI and HS administered the project. YF, TN, ST, KN and AI provided resources. MA, AI and HS supervised the study. YF, ST, KN, SS, AI and HS performed validation. YF, ST, KN and HN performed visualization. YF wrote the original draft. All authors reviewed and edited the manuscript.

Conflicts of interest

YF and HS hold a patent on the use of Muse cells for treating EB. OW is an employee of Life Science Institute, Inc. (LSII). AI and HS received a research grant from LSII. YF and HS received medical advisor fees from LSII.

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Characterization of non-responders to interleukin-17 inhibitors in moderate to severe psoriasis patients enrolled in the Corrona® Psoriasis Registry

Dear Editor,

While interleukin-17 (IL-17) inhibitors are effective for many patients with psoriasis, there are limited real-world data characterizing patients who respond or do not respond to this biologic class.[1] The identification of patient characteristics associated with response to this class of medication would present a significant advantage for both patients and physicians. For this reason, we have conducted a retrospective characterization of non-response to IL-17 inhibitors in patients with moderate-to-severe psoriasis.

Data were collected from patients enrolled in the Corrona Psoriasis Registry (the largest independent observational registry of psoriasis patients in North America) that had moderate-to-severe psoriasis [body surface area (BSA) ≥3%] treated with IL-17 inhibitors. A total of 533 patients with 6-month follow-up of IL-17 inhibitor use were identified. Response was defined as movement to mild disease severity, defined as BSA <3% or 75% improvement in BSA (BSA75) at 6-month follow-up. Statistical tests (*t*-tests/chi-squared tests/Fisher's exact tests) were used to compare means and frequencies of baseline characteristics categorized by response (n = 308) vs. non-response (n = 225) at 6 months. Compared with responders, non-responders were more likely to be current (19% vs. 12%) or former smokers (40% vs. 34%) and have a history of diabetes mellitus (24% vs. 14%); all $P < 0.05$. Non-responders were also more likely to have previously received two (25% vs. 20%) or ≥3 (33% vs. 18%) biologics ($P < 0.001$; Table 1).

Current and past cigarette usage were the only lifestyle characteristics found to occur with greater frequency in IL-17 inhibitor non-responders. The link between smoking and psoriasis is well known, with one large meta-analysis showing an odds ratio of 1.84 increased odds for development of psoriasis in smokers when compared to non-smokers.[2] Additionally, two previous studies assessing clinically predictive markers for tumour necrosis factor α (TNF-α) inhibitor response found that current cigarette use was also associated with non-response in psoriasis and rheumatoid arthritis patients.[3,4] This finding may serve as a reminder that providers should always encourage patients to discontinue smoking and provide assistance or refer when appropriate.

In this study, non-responders were more likely to more often report a history of multiple biologics when compared to those that had an adequate response. These patients may represent serial non-responders with a unique subset of psoriasis, requiring an alternative target for disease remission. Baseline patient-reported outcome measures [Dermatology Life Quality Index (DLQI), Work Productivity and Activity Impairment (WPAI), itch, fatigue, skin pain, EQ-5D-3L] were not statistically significantly different between responders and non-responders. These findings are in line with a previous study looking at characteristics of non-responders to TNF-α inhibitors, which showed no association with biologic response and baseline disease activity.[5]

These real-world findings provide novel information regarding characteristics of responders and non-responders to IL-17 inhibitors. Further analysis with a larger sample size may be useful in helping to characterize patients that will benefit from IL-17 inhibitors. Findings from this observational study may be useful in helping clinicians determine baseline characteristics

