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Long-term efficacy and safety of intravenous injection of clonal mesenchymal stem cells derived from bone marrow in five adults with moderate to severe atopic dermatitis

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Abstract

Atopic dermatitis is a chronic and relapsing inflammatory skin disease that is treated with immunosuppressants. However, long-term use of immunosuppressants may cause toxicity and severe side-effects. To confirm the long-term efficacy and safety of clonal mesenchymal stem cell therapy, we performed investigator-initiated clinical trials and long-term observation in five adult patients with moderate to severe atopic dermatitis that was refractory to conventional treatments. The clinical response assessment values such as Eczema Area and Severity Index (EASI) improved significantly at 16 weeks, and 80% (4/5) of the patients achieved EASI-50 after one or two treatment cycles. Patients were observed for long-term efficacy and safety for an average of 38 weeks (range, 16–86) and showed no serious side-effects. Among the cytokines tested, CCL-17, interleukin (IL)-13, and IL-22 significantly decreased at the end-point of the five participants, two patients who maintained good clinical response over 84 weeks showed increased IL-17 cytokine levels in the blood.

KEYWORDS

allogeneic clonal, long-term efficacy and safety, mesenchymal stem cell, stem cell therapy, the atopic dermatitis

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease accompanied by severe itching and shows heterogeneous phenotypes. In addition to cutaneous symptoms, many studies have reported that moderate to severe AD significantly affects a patient's emotional and psychological well-being.^{1,2} AD is a major public health burden worldwide, with a lifetime prevalence of 10–20% in children and 3–7% in adults.^{3–6}

The treatment of AD varies according to the severity of the disease, with severe cases needing systemic immunosuppressants.⁷ However, long-term use of immunosuppressants may cause severe toxicity and side-effects. Biologics that target a specific cytokine

show long-term safety and efficacy in patients with moderate to severe AD;⁸ however, the proportion of patients who have not achieved complete or nearly complete disease elimination is still high.^{2,9} Moreover, those drugs should be used through multiple administrations to achieve sufficient efficacy.

Mesenchymal stem cells (MSC) are undifferentiated, and multipotent cells have immunomodulatory and immune inhibitory properties.^{10,11} Therefore, MSC have been used as therapeutic agents in autoimmune and chronic inflammatory diseases such as graft-versus-host disease, Crohn's disease, refractory systemic lupus erythematosus, and systemic sclerosis.¹² A few studies have reported the effect of MSC therapy on inflammatory skin conditions in experimental animal models and clinical samples.^{13–15} However, reports on long-term efficacy and safety of MSC therapy for AD are still limited.

Hyun-Tae Shin and Si Hyub Lee contributed equally to this work.

We performed an investigator-initiated clinical trial to demonstrate the efficacy and safety of multiple doses of allogeneic bone marrow-derived clonal MSC in five adult patients with moderate to severe AD that was refractory to the conventional treatments. Furthermore, we conducted long-term observation of the patients to confirm the long-term efficacy and safety of clonal MSC therapy and analyzed cytokine biomarkers in the blood of the participants.

2 | METHODS

2.1 | Investigator-initiated clinical trial design

A single-center, open-labeled, investigator-initiated clinical trial for the therapeutic use of allogeneic bone marrow-derived clonal MSC (SCM Lifescience) in adults with moderate to severe AD was conducted with prior approval from the Korean Ministry of Food and Drug Safety. The isolation protocol, called the sub-fractionation culturing method (SCM), was applied to generate single bone marrow cell-derived clonal MSC for this trial.^{16,17} The multipotency including the capacity to differentiate into the three major mesenchymal lineages (osteoblasts, adipocytes, and chondrocytes) and the expression pattern of specific cell surface markers of general MSC were confirmed in all clonal MSC lines utilized in this trial. The trial was conducted over a period of 16 weeks (treatment for 4 weeks and follow-up for 12 weeks) and was followed by an observation period. In this clinical trial, 1.0×10^6 cells/kg dose of SCM-CGH (fresh stem cell product) or SCM-AGH (frozen stem cell product) (SCM Lifescience) was administrated intravenously three times every 2 weeks at 2–4.5 mL/min infusion rate to enrolled patients. Participants were enrolled with an individual protocol for fresh or frozen form and one patient (S004) was injected with the frozen form of clonal MSC for two cycles while the other patients were injected with the fresh form. Concomitant medications such as corticosteroid-free emollients, low-potency (groups 6 and 7) topical corticosteroids, antihistamines, or anti-inflammatory drugs were permitted during study participation. Other detailed of the study design are in the Supplemental Study Protocol.

After 16 weeks of the trial, we followed up to confirm the period during which the patient's improved symptoms are maintained by oral antihistamines and/or topical medications including low-potency (groups 6 and 7) topical corticosteroids without additional use of systemic steroids and systemic immunomodulators. Long-term safety and effectiveness were evaluated every 2 months. If the symptoms worsened during follow-up in patients who had improved clinical symptoms during the trial cycle, an additional cycle of treatments was conducted. Evaluation and follow-up of the additional cycle of treatments was conducted in the same way as the first trial.

2.2 | Participants

This clinical trial included healthy adults with moderate to severe AD diagnosed according to the criteria of Hanifin and Rajka.¹⁸ The

inclusion criteria included moderate to severe AD (Scoring Atopic Dermatitis [SCORAD] > 20), age from 20 to 60 years, and persistent symptoms (≥ 6 months). The exclusion criteria are in the Supplemental Study Protocol.

2.3 | Measurement of cytokine biomarkers

During the treatment cycle and follow-up period, blood was collected, allowed to clot at room temperature for 30 min, and then centrifuged for 10 min at 400 g. Serum samples were aliquoted, frozen at -80°C , and thawed immediately prior to analysis. Quantification of CCL-17 (thymus- and activation-regulated chemokine), CCL-22 (MDC), interleukin (IL)-13, IL-17, IL-18, IL-22 (R&D Systems), and immunoglobulin (Ig)E (Thermo Fisher Scientific) was performed by enzyme-linked immunosorbent assay (ELISA) with the appropriate dilution factor (Table S1). All measurements were performed in duplicate. The ELISA kits were used according to the manufacturer's instruction. Optical densities were measured at 450 nm with wavelength correction at 540 nm using a Gen5 Microplate Reader (BioTek Instruments).

2.4 | Statistical analyses

Statistical analyses were performed using R software version 3.6.0 (R Foundation). Wilcoxon signed-rank test was performed to evaluate the statistical significance of the change in clinical and experimental assessment values between the scores documented at the baseline visit and the end-point. For statistical tests, the level of significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Characteristics of patients

This clinical trial included five patients who did not respond to conventional treatments (Table S2). The mean age of the patients was 23 years (range, 20–29). The trial included 60% (3/5) men and 40% (2/5) women. No patient reported any other current medical condition in addition to AD. The mean Eczema Area and Severity Index (EASI) was 31.5 (range, 15.5–40.0) at the baseline, and mean SCORAD was 66.2 (range, 51.0–76.1). All patients completed one cycle of the clinical trial, and except S001, four patients were subjected to a second cycle due to exacerbation of AD.

3.2 | Improvement of AD using clonal MSC

All primary efficacy end-points including a mean reduction of EASI, SCORAD, body surface area (BSA), and Investigator Global Assessment (IGA) in both cycles were statistically significant (Figure 1a and Table S3). Both cycles were treated using the same protocol, and only S005

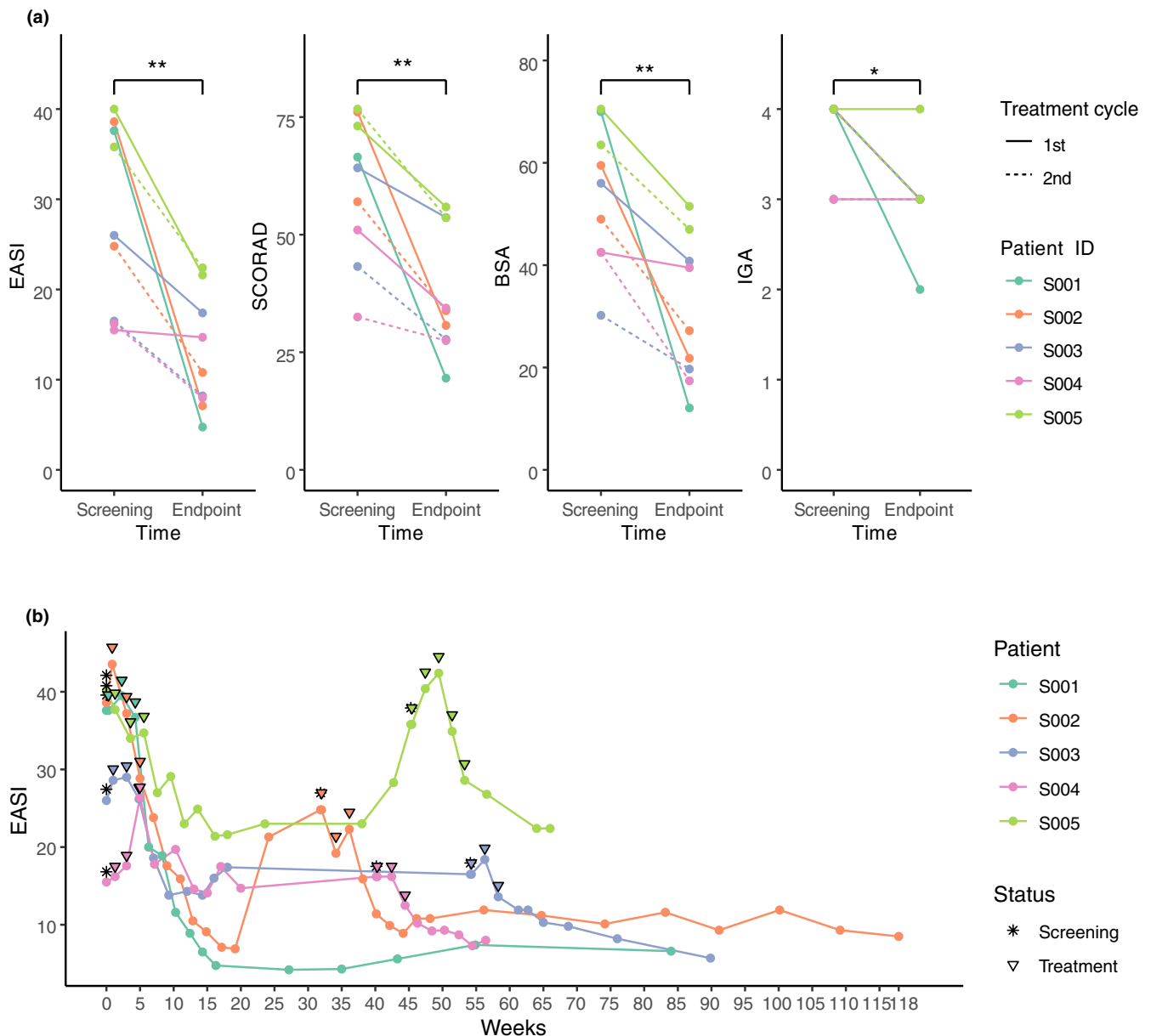


FIGURE 1 Clinical response of patients with atopic dermatitis to clonal mesenchymal stem cell therapy. (a) Comparison of clinical response between screening and end-point (followed up at ~16 weeks). The significance of the results was evaluated with Wilcoxon signed-rank test. BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; SCORAD, Scoring Atopic Dermatitis. (b) Changes in Eczema EASI score of atopic dermatitis patients treated with clonal mesenchymal stem cells. ** $p < 0.01$, * $p < 0.05$

in the second cycle received two additional injections of MSC due to exacerbation of AD symptoms during the injection period. EASI reduction at the end-point for each patient were as follows: S001, 87% in the first cycle; S002, 82% in the first cycle and 56% in the second cycle; S003, 33% in the first cycle and 50% in the second cycle; S004, 5% in the first cycle and 51% in the second cycle; and S005, 46% in the first cycle and 37% in the second cycle. S001 achieved more than 50% reduction in EASI (EASI-50 response) in the first cycle (Figure S2), and S002 achieved EASI-50 response in both cycles (Figures S3 and S4). S003 and S004 did not achieve EASI-50 response in the first cycle, but achieved it in the second cycle. S005 did not achieve EASI-50 response in both cycles. For secondary efficacy end-points, a reduction in eosinophil count

and eosinophil cationic protein was observed, but it was not statistically significant, and total IgE in the undiluted serum was similar at the end of both cycles (Figure S1 and Table S3). Most primary and secondary end-points were evaluated at 12 weeks after clonal MSC therapy, and only those of the additional cycle for S003 were evaluated at 17 weeks.

3.3 | Long-term efficacy and safety of MSC therapy

Participants were followed up for an average of 38 weeks (range, 16–86) after screening to check how long the improved symptoms were

maintained without additional use of systemic steroids and systemic immunomodulators (Figure 1b). S001, who underwent only the first cycle treatment, maintained the EASI-50 response for 84 weeks (Figures 1b and 2a). Interestingly, S002, who improved with the first cycle treatment and worsened during follow-up, maintained the EASI-50 response for 86 weeks after screening of the second cycle (Figures 1b and 2b). S001 and S005 were lost to follow-up observation after the last visit, and S002 continued to present an improved status. During the observation period, S003 and S004 presented exacerbated symptoms, and the observation was discontinued due to the use of systemic steroids or systemic immunomodulators.

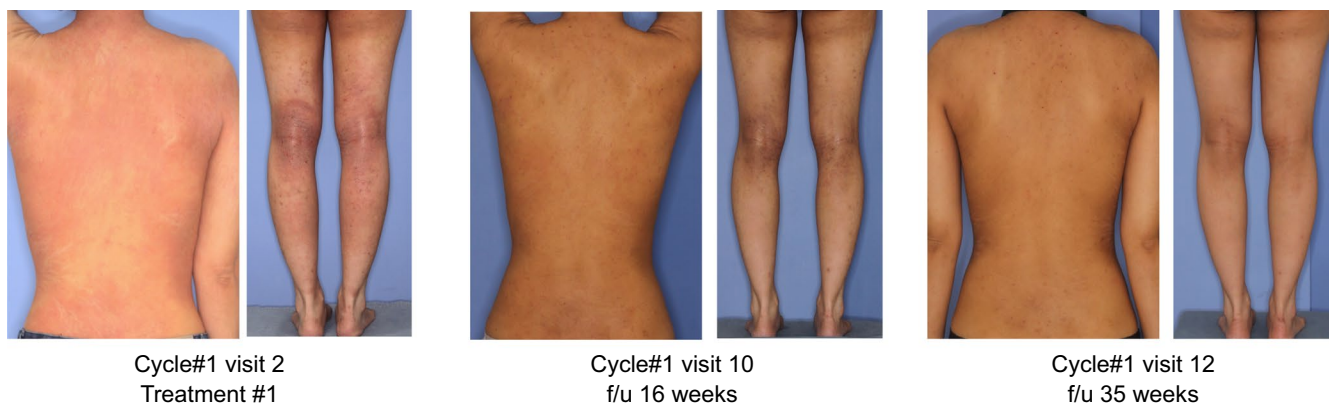
There were no serious adverse events associated with MSC therapy in long-term observation. S001 had acute upper respiratory tract infection (URI) and otitis externa during the trial cycle and recovered completely within 2 weeks. S002 also had acute URI and recovered completely within 2 weeks. S003 had cellulitis on the right ankle 4 weeks after MSC injection, which improved after oral antibiotic treatment for 29 days. S005 had intermittent non-specific chest pain lasting approximately 10 min during the injection period, which improved without special treatment. Local inflammatory reaction, skin rash, urticaria and so forth did not occur at the injection site during the administration of MSC. Severe allergic reactions such

as shortness of breath, wheezing, sudden changes in blood pressure, palpitations, and side-effects due to vascular blockage after i.v. administration did not occur.

3.4 | Cytokine biomarkers in response to treatment

We measured several biomarkers (CCL-17, CCL-22, IL-13, IL-18, IL-22, and IgE) using ELISA with the appropriate dilution factor (Table S1). CCL-17, IL-13, and IL-22 significantly decreased at the end-point, and other biomarkers showed decreasing trends during the experiments (Figure 3 and Table S4). As a result of measuring IgE, difference was not observed in the pre- and post-treatment groups in total IgE in the undiluted serum (Figure S1), but as a result of measuring IgE by diluting the serum, a decrease in IgE was clearly observed in patients 1 and 2, whose symptoms were clearly improved (Figure 3 and Table S4). Interestingly, S001 and S002 achieved EASI-50 response in the first cycle treatment and maintained long-term efficacy from screening (S001, for 84 weeks after the first cycle treatment; S002, for 86 weeks after the second cycle treatment) and showed relatively high levels of IL-17 in their blood than the other patients.

(a)



(b)

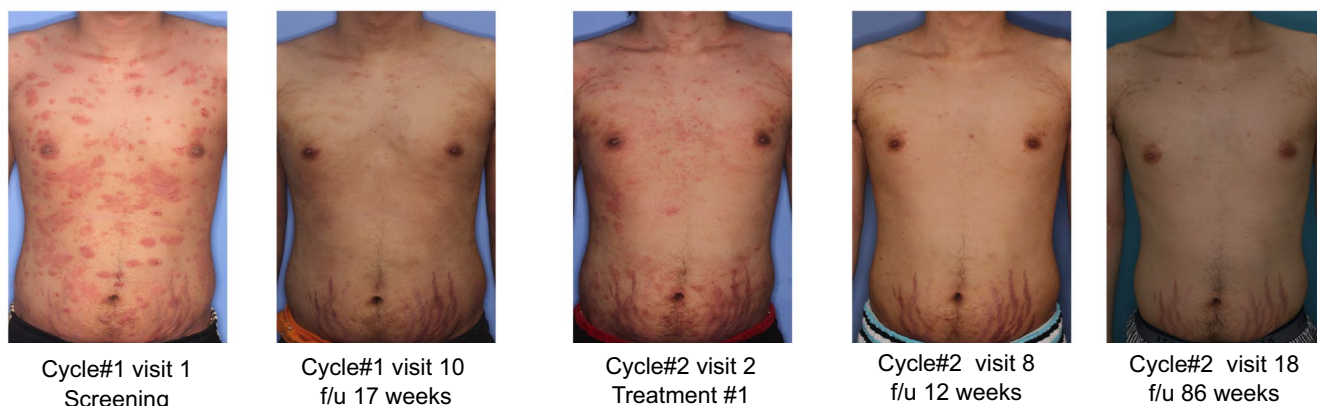


FIGURE 2 Photographs of atopic dermatitis patients with good long-term response to clonal mesenchymal stem cell therapy. (a) S001 patient. (b) S002 patient. f/u, follow-up

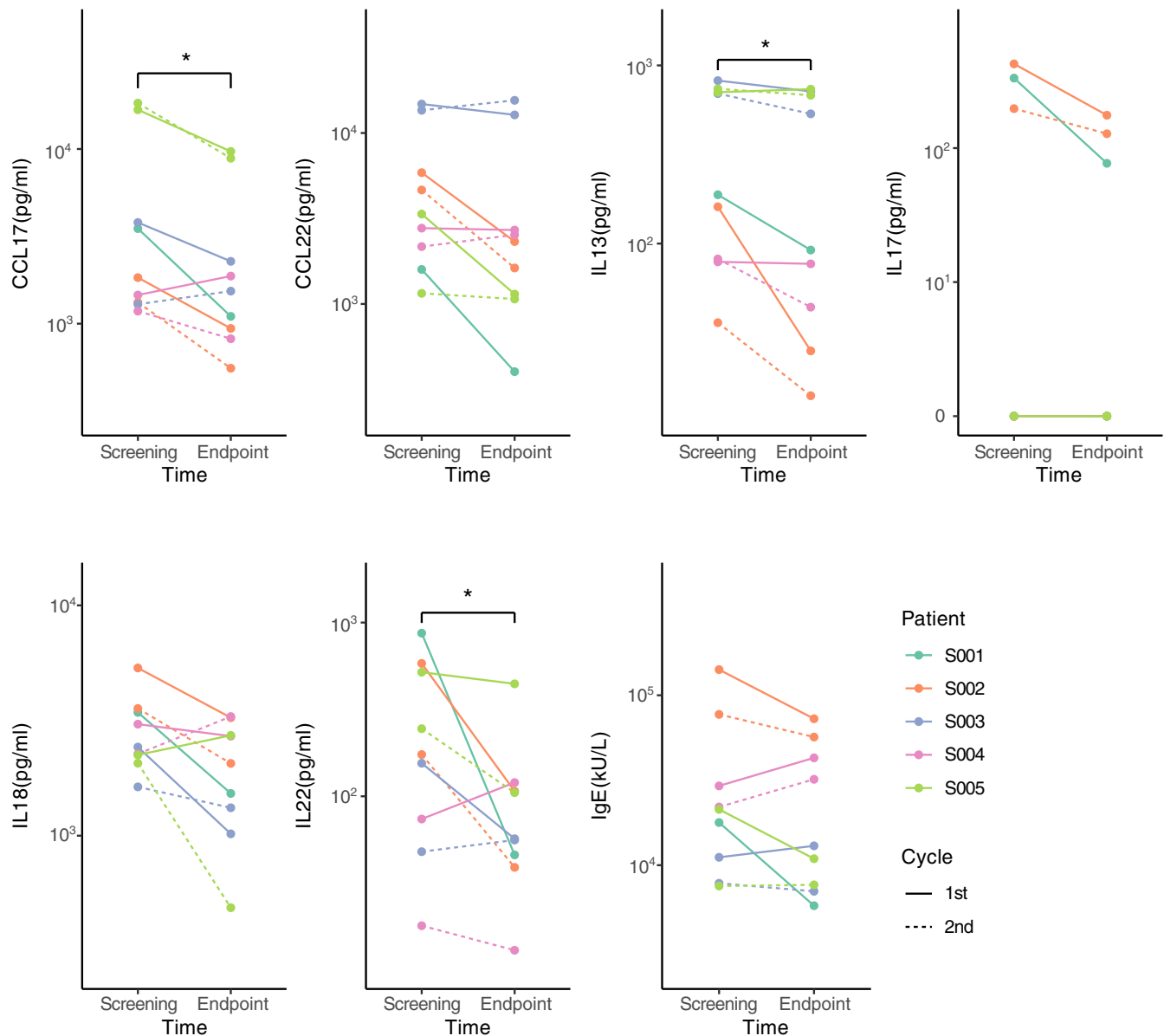


FIGURE 3 Comparison of biomarkers of atopic dermatitis in response to clonal mesenchymal stem cell therapy between screening and end-point (followed up at ~16 weeks). The significance of the results was evaluated with Wilcoxon signed-rank test. * $p < 0.05$

4 | DISCUSSION

To demonstrate the efficacy and safety of multiple doses of allogeneic clonal MSC derived from bone marrow, we performed an investigator-initiated clinical trial in five adult patients with moderate to severe AD refractory to the conventional treatments and observed the patients to confirm the long-term efficacy and safety of clonal MSC therapy. The EASI, SCORAD, BSA, and IGA of the patients improved significantly after approximately 16 weeks and 80% (4/5) of the patients achieved EASI-50 after one or two cycles of treatment. Patients were observed for efficacy and safety for an average of 38 weeks (range, 16–86) and showed no serious side-effects. Among the participants, two patients were shown to maintain long-term (S001, 84 weeks; and S002, 86 weeks) efficacy

without systemic steroids and immunomodulators, and increased levels of IL-17 cytokine in blood circulation.

Engraftment and transdifferentiation, immunomodulatory effect, and paracrine effects of exosomes containing various functional factors have been suggested as mechanisms underlying the therapeutic effect arising from MSC administration.^{19,20} Although MSC can be differentiated into specific tissues, there is a lot of controversy over whether MSC are engrafted to patients' tissues when administrated i.v.²⁰ Autopsy studies of patients who died after administration of MSC have reported a tendency to decrease implanted MSC with increase in the period between dosing and autopsy.²¹ However, despite the temporary presence of the administrated MSC in the recipients, it is presumed that the degree of engraftment and maintenance of the initial MSC and changes in

the microenvironment of the engrafted tissues affect the treatment response, considering that the effect persisted over a relatively long period of time in our study. In our previous ovalbumin-induced AD animal model study, we demonstrated that i.v. injected clonal MSC were capable of suppressing AD via inhibition of IL-4 and IgE production in T cells and B cells, respectively. In addition, clonal MSC migrated to draining lymph nodes near the inflamed skin lesion that may result in the inhibition of effector cell migration.²² The long-term effects observed in the patients included in this study may suggest that the immune system of the patients can return to the normal state after MSC administration, and further study of the mechanisms is needed.

Atopic dermatitis appears to be a relatively heterogeneous disease that is driven by both T-helper (Th)2 and Th22, with variable Th1 and Th17 activation.^{23,24} Novel IL-4R (Th2)-targeting agents such as dupilumab for AD showed significant improvement, but the proportion of patients who have not achieved complete or nearly complete disease elimination is still high.^{2,9,23} Studies with Asian AD, early-onset pediatric AD, and intrinsic AD reported higher IL-17 expression in their cohort.^{25–27} In this clinical trial, two patients (S001 and S002) responded well to MSC therapy and had relatively high IL-17 (Th17) cytokine levels (Figure 3). Some cancer studies have described a connection between the Th17 cell-related cytokines and cancer stem cells (CSC) and reported that IL-17 could contribute to CSC maintenance and stimulate their self-renewal.^{28,29} In this regard, MSC therapy has the potential to be a good therapeutic option for moderate to severe AD with high IL-17 levels.

The limitation of this study is that a small number of patients with AD were enrolled in the clinical trial. Therefore, large-scale clinical trials are necessary to confirm the long-term efficacy and safety for moderate to severe AD. Moreover, we did not control the type of clonal MSC lines for AD treatment (Table S2). Although all clonal cell lines had similar properties to general MSC, the variation in response due to changes in cell lines could not be ruled out.

Through this clinical trial, we provide some evidence for the long-term efficacy and safety of clonal MSC therapy in moderate to severe AD patients without serious adverse events and suggest that high IL-17 levels may be associated with good clinical improvement with MSC therapy.

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CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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