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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TITLE PAGE

Title: 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 weeks) and showed no serious side effects. Among the cytokines tested, CCL-17, IL-13 and IL-22 significantly decreased at the endpoint of the five participants, two patients who maintained good clinical response over 84 weeks showed increased IL-17 cytokine levels in the blood.

KEY WORDS

Atopic dermatitis, Mesenchymal stem cell, Long-term efficacy and safety

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 treated through multiple administrations to achieve sufficient efficacy.

Mesenchymal stem cells (MSCs) are undifferentiated, and multipotent cells have immunomodulatory and immune inhibitory properties.[10, 11] Therefore, MSCs 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, 14] However, reports on long-term efficacy and safety of MSC therapy for AD are still limited.

We performed an investigator-initiated clinical trial to demonstrate the efficacy and safety of multiple doses of allogeneic bone marrow-derived clonal MSCs 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.

MATERIALS AND METHODS

Investigator-initiated clinical trial design

A single-center, open-labeled investigator-initiated clinical trial for the therapeutic use of allogeneic bone marrow-derived clonal MSCs (SCM Lifesciences Co. Ltd., Incheon, Republic of Korea) in adults with moderate to severe AD was conducted with prior approval from the Korean Ministry of Food and Drug Safety. 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 Lifesciences Co. Ltd., Incheon, Republic of Korea) was administered intravenously 3 times every 2 weeks at 2–4.5 mL/min infusion rate to enrolled patients. One patient (S004) was injected with the frozen form of clonal MSCs for two cycles while the other patients were injected with the fresh form. 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 MSCs were confirmed in all clonal MSC lines utilized in this trial. Other detailed of the study design are in 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 without additional use of systemic steroids and systemic immunomodulators. Long-term safety and

effectiveness were evaluated every two 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.

Participants

This clinical trial included healthy adults with moderate to severe AD diagnosed according to the criteria of Hanifin and Rajka.[15] 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 Supplemental Study Protocol.

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 $\times$ g. Serum samples were aliquoted, frozen at -80°C, and thawed immediately prior to analysis. Quantification of CCL-17 (TARC), CCL-22 (MDC), IL-13, IL-17, IL-18, IL-22 (R&D Systems, Inc., Minneapolis, MN, USA), and IgE (Thermo Fisher Scientific Inc., Waltham, MA, USA) was performed by enzyme-linked immunosorbent assay (ELISA) with the appropriate dilution factor (**Supplementary Table 1**). 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 Inc., Winooski, VT, USA).

Statistical analyses

Statistical analyses were performed using R software version 3.6.0 (R Foundation, Vienna, Austria). 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 endpoint. For statistical tests, the level of significance was set at $p < 0.05$.

RESULTS

Characteristics of patients

This clinical trial included five patients who did not respond to conventional treatments (**Supplementary Table 2**). The mean age of the patients was 23 years (range: 20–29 years). 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 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.

Improvement of AD using clonal MSCs

All primary efficacy endpoints including a mean reduction of EASI, SCORAD, BSA (body surface area), and IGA (investigator global assessment) in both cycles were statistically significant (**Figure 1A and Supplementary Table 3**). Both cycles were treated using the same protocol, and only S005 in the second cycle received two additional injections of MSCs due to exacerbation of AD symptoms during the injection period. EASI reduction at the endpoint for each patient were as follows, S001: 87% in the 1st cycle; S002: 82% in the 1st cycle and 56% in

the 2nd cycle; S003: 33% in the 1st cycle and 50% in the 2nd cycle; S004: 5% in the 1st cycle and 51% in the 2nd cycle; and S005: 46% in the 1st cycle and 37% in the 2nd cycle. S001 achieved more than 50% reduction in EASI (EASI-50 response) in the first cycle, and S002 achieved EASI-50 response in both cycles. 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 endpoints, a reduction in eosinophil count and ECP was observed, but it was not statistically significant, and total IgE in the undiluted serum was similar at the end of both cycles (**Supplementary Figure 1 and Supplementary Table 3**). Most primary and secondary endpoints were evaluated at 12 weeks after clonal MSC therapy, and only those of the additional cycle for S003 were evaluated at 17 weeks.

Long-term efficacy and safety of MSC therapy

Participants were followed up for an average of 38 weeks (range: 16–86 weeks) 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 (**Figure 1B and Figure 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 (**Figure 1B and Figure 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 two weeks. S002 also had acute URI and recovered completely within two 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 about 10 min during the injection period, which improved without special treatment. Local inflammatory reaction, skin rash, urticaria, etc., did not occur at the injection site during the administration of MSCs. Severe allergic reactions such as shortness of breath, wheezing, sudden changes in blood pressure, palpitations, and side effects due to vascular blockage after intravenous administration did not occur.

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 (**Supplementary Table 1**). CCL-17, IL-13, and IL-22 significantly decreased at the endpoint, and other biomarkers showed decreasing trends during the experiments (**Supplementary figure 2 and Supplementary Table 4**). 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.

DISCUSSION

178 To demonstrate the efficacy and safety of multiple doses of allogeneic clonal MSCs derived
179 from bone marrow, we performed an investigator-initiated clinical trial in five adult patients
180 with moderate to severe AD refractory to the conventional treatments and observed the patients
181 to confirm the long-term efficacy and safety of clonal MSC therapy. The EASI, SCORAD, BSA,
182 and IGA of the patients improved significantly after about 16 weeks and 80% (4/5) of the
183 patients achieved EASI-50 after one or two cycles of treatment. Patients were observed for
184 efficacy and safety for an average of 38 weeks (range: 16–86 weeks) and showed no serious side
185 effects. Among the participants, two patients were shown to maintain long-term (S001: 84 weeks
186 and S002: 86 weeks) efficacy without systemic steroids and immunomodulators, and increased
187 levels of IL-17 cytokine in blood circulation.

188 AD appears to be a relatively heterogeneous disease that is driven by both Th2 and Th22, with
189 variable Th1 and Th17 activation.[16, 17] Novel IL-4R (Th2)-targeting agents such as
190 dupilumab for AD showed significant improvement, but the proportion of patients who have not
191 achieved complete or nearly complete disease elimination is still high. [2, 9, 16] Studies with
192 Asian AD, early-onset pediatric AD, and intrinsic AD reported higher IL-17 expression in their
193 cohort.[18-20] In this clinical trial, two patients (S001 and S002) responded well to MSC therapy
194 and had relatively high IL-17 (Th17) cytokine levels (**Figure 3**). Some cancer studies have
195 described a connection between the Th17 cell-related cytokines and cancer stem cells (CSCs)
196 and reported that IL-17 could contribute to CSCs maintenance and stimulate their self-
197 renewal.[21, 22] In this regard, MSC therapy has the potential to be a good therapeutic option for
198 moderate to severe AD with high IL-17 levels.

199 The limitation of this study is that a small number of patients with AD were enrolled in the
200 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 (**Supplementary table 2**). Although all clonal cell lines had similar properties to general MSCs, 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.

LEGENDS

Figure 1. Clinical response of patients with atopic dermatitis to clonal mesenchymal stem cell therapy. (A) Comparison of clinical response between screening and endpoint (followed up at about 16 weeks). The significance of the results was evaluated with Wilcoxon signed-rank test. EASI: Eczema Area and Severity Index, SCORAD: SCORing Atopic Dermatitis, BSA: Body Surface Area, IGA: Investigator Global Assessment. (B) Changes in Eczema Area and Severity Index (EASI) score of atopic dermatitis patients treated with clonal mesenchymal stem cells. $**p < 0.01$, $*p < 0.05$

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.

Supplementary figure 1. Comparison of laboratory response of atopic dermatitis to clonal mesenchymal stem cell therapy between screening and endpoint (followed up at about 16 weeks). The significance of the results was evaluated with Wilcoxon signed-rank test. ECP: Eosinophil Cationic Protein

Supplementary figure 2. Comparison of biomarkers of atopic dermatitis in response to clonal mesenchymal stem cell therapy between screening and endpoint (followed up at about 16 weeks). The significance of the results was evaluated with Wilcoxon signed-rank test. $*p < 0.05$

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232

233 **LIST OF ABBREVIATIONS**

234 EASI: eczema area and severity index

235 AD: atopic dermatitis

236 MSCs: mesenchymal stem cells

237 SCORAD: scoring atopic dermatitis

238 ELISA: enzyme-linked immunosorbent assay

239 URI: upper respiratory tract infection

240 CSCs: cancer stem cells

241 BSA: body surface area

242 IGA: investigator global assessment

243

244 **DECLARATIONS**

245 **Ethics approval and consent to participate**

246 This investigator-initiated clinical trial for each participant was reviewed and approved by the
247 institutional review board of Inha University Hospital [IRB No. 2017-06-009, 2017-12-015,
248 2017-09-019, 2018-04-031, 2018-05-005, 2018-12-005, 2018-12-032], and was performed in
249 accordance with the principles of the Declaration of Helsinki, Korean Good Clinical Practice

guidelines, and local regulatory requirements. All patients provided informed consent prior to participation.

Consent for publication

Consent for publication was obtained from participants of the clinical trial.

Availability of data and materials

All data analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

H.-T.S. and S.H.L. performed all analysis of data and writing the manuscript with guidance from G.S.C.. S.H.L. performed enrollment of participants and the treatment of trial drugs. S.H.L.,

H.S.Y., J.H.H., S.B.L., J.W.B., J.S., and G.S.C. contributed to clinical data collection. Y.-K.C., M.-S.J., E.C., and S.U.S. contributed to experimental data collection. S.H.L. J.W.B., J.S., S.U.S., and G.S.C. contributed to study design. H.-T.S. and S.H.L. contributed equally to this work. All authors reviewed the manuscript.

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Figure 1

A

B

Figure 2

A

B

Sup figure 1

Sup figure 2

Supplementary table 1. Dilution factor of biomarkers

Biomarker	Dilution factor
CCL-17 (TARC)	10
CCL-22 (MDC)	20
IL-13	2
IL-17	1
IL-18	20
IL-22	1
Total IgE	500-1000

Supplementary table 2. Characteristics of the participants at baseline.

Case	Sex/Age	Previous treatments
1	F/24	Allergen-specific immunotherapy, Cyclosporine, Topical corticosteroids, Topical calcineurin inhibitors
2	M/21	Systemic steroids, Cyclosporine, Topical corticosteroids, Topical calcineurin inhibitors
3	F/29	Systemic steroids, Phototherapy, Cyclosporine, Topical corticosteroids, Topical calcineurin inhibitors
4	M/20	Systemic steroids, Phototherapy, Cyclosporine, Topical corticosteroids, Topical calcineurin inhibitors
5	M/21	Systemic steroids, Phototherapy, Cyclosporine, Topical corticosteroids, Topical calcineurin inhibitors

EASI: Eczema Area and Severity Index

SCORAD: Severity Scoring for Atopic Dermatitis

EASI	SCORAD
37.6	66.5
38.6	76.1
26	64.2
15.5	51
40	73.1

Supplementary table 3. Clinical response measures and biomarker levels

Patient ID.		Visit 1	Visit 2	Visit 3	Visit 4
		2017.07.12	2017.07.14	2017.07.28	2017.08.11
		Cycle1_Screening	Cycle1_Tx1	Cycle1_Tx2	Cycle1_Tx3
	MSCs cell-line ID		A0408 D13	A0106 D126	A0106 D126
S001	BSA	70	70	69	62.5
	EASI	37.6	37.6	39.5	36.7
	SCORAD	66.5	66.5	69.8	65.5
	IGA	4	4	4	4
	Eosinophil count	2053	2406	2503	2618
	Total IgE	5000	5000	5000	5000
	ECP	200	200	200	200
		2017.11.16	2017.11.22	2017.12.07	2017.12.21
		Cycle1_Screening	Cycle1_Tx1	Cycle1_Tx2	Cycle1_Tx3
	MSCs cell-line ID		A0106 D126	A0106 D127	A0106 D127
S002	BSA	59.5	71.5	70.5	61.5
	EASI	38.6	43.55	37.2	28.85
	SCORAD	76.1	80.3	73.6	60.9
	IGA	4	4	4	4
	Eosinophil count	1096	1643	1469	780
	Total IgE	5000	-	5000	5000
	ECP	110	-	91.3	138
		2018.05.02	2018.05.09	2018.05.23	2018.06.05
		Cycle1_Screening	Cycle1_Tx1	Cycle1_Tx2	Cycle1_Tx3
	MSCs cell-line ID		A0102 D201	A0106 D126	A0108 D203
S003	BSA	56	63	61.3	58.3
	EASI	26	28.6	29	26.2
	SCORAD	64.2	69.1	68.76	65.66
	IGA	4	4	4	4
	Eosinophil count	768	1519	1513	825
	Total IgE	5000	-	5000	5000
	ECP	118	-	122	105
		2018.05.15	2018.05.24	2018.06.05	2018.06.19
		Cycle1_Screening	Cycle1_Tx1	Cycle1_Tx2	Cycle1_Tx3
	MSCs cell-line ID		A0106 D127	A0106 D127	A0106 D127
S004	BSA	42.5	45.3	48.8	62
	EASI	15.5	16.2	17.6	26.4
	SCORAD	51	51.06	48.56	62.7
	IGA	3	3	3	4
	Eosinophil count	392	473	668	847

	Total IgE	2481	-	2540	2514
	ECP	0	-	0	0
		2018.05.21	2018.05.30	2018.06.15	2018.06.29
		Cycle1_Screeni	Cycle1_Tx1	Cycle1_Tx2	Cycle1_Tx3
	MSCs cell-line ID		A0106 D127	A0106 D127	A0106 D127
	BSA	70.5	70	69	68.5
S005	EASI	40	37.7	34	34.7
	SCORAD	73.1	68.5	73.8	64.8
	IGA	4	4	4	4
	Eosinophil count	1805	1813	2162	1383
	Total IgE	5000	-	5000	5000
	ECP	200	-	200	200

BSA: Body Surface Area

EASI: Eczema Area and Severity Index

SCORAD: Severity Scoring for Atopic Dermatitis

IGA: Investigator Global Assessment

ECP: Eosinophil Cationic Protein

Tx: Treatment

FU: Follow-up

Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
2017.08.25 Cycle1_FU	2017.09.08 Cycle1_FU	2017.09.22 Cycle1_FU	2017.10.07 Cycle1_FU	2017.10.20 Cycle1_FU	2017.11.03 Cycle1_FU
46.5	34.9	23.5	20.1	18.1	12.1
20	18.9	11.6	8.9	6.5	4.75
52.3	43.48	32.2	23.52	24.12	19.5
3	3	3	3	2	2
1998	1505	-	666	-	628
5000	-	-	-	-	4928
200	-	-	-	-	104
2018.01.04 Cycle1_FU	2018.01.18 Cycle1_FU	2018.02.01 Cycle1_FU	2018.02.14 Cycle1_FU	2018.02.28 Cycle1_FU	2018.03.16 Cycle1_FU
52.5	43	40	27.1	25.6	21.8
23.8	17.6	15.9	10.5	9.1	7.1
55.1	40.8	40.6	32.9	30.6	30.7
4	3	3	3	3	3
696	749	-	732	-	1085
5000	-	-	-	-	5000
131	-	-	-	-	108
2018.06.20 Cycle1_FU	2018.07.06 Cycle1_FU	2018.07.25 Cycle1_FU	2018.08.10 Cycle1_FU	2018.08.22 Cycle1_FU	2018.09.05 Cycle1_FU
41.3	32.8	35.4	31	32	40.8
18.6	13.8	14.3	13.8	16	17.4
48.76	42.56	48.98	48.2	50.2	53.66
3	3	3	3	3	3
741	406	-	672	-	420
5000	-	-	-	-	5000
73.2	-	-	-	-	38
2018.07.04 Cycle1_FU	2018.07.26 Cycle1_FU	2018.08.14 Cycle1_FU	2018.08.28 Cycle1_FU	2018.09.11 Cycle1_FU	2018.10.02 Cycle1_FU
43.4	51.3	42.1	40.9	40.4	39.5
17.8	19.7	14.6	14.1	17.5	14.7
41.68	42.96	37.42	35.38	37.28	34.4
3	3	3	3	3	3
684	781	-	318	-	430

2794	-	-	-	-	3317
0	-	-	-	-	0
2018.07.13	2018.07.27	2018.08.10	2018.08.24	2018.09.11	2018.09.24
Cycle1_FU	Cycle1_FU	Cycle1_FU	Cycle1_FU	Cycle1_FU	Cycle1_FU
60	63	56	58	47	51.5
27	29.1	23	24.9	21.4	21.6
61.8	56.7	57.7	57.4	49.5	55.9
4	4	4	4	4	4
896	944	-	889	-	664
5000	-	-	-	-	5000
200	-	-	-	-	138

Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
2018.01.18	2018.03.14	2018.05.11	2018.07.31	2019.02.20	
FU	FU	FU	FU	FU	
11.3	12.5	18	15	15.5	
4.2	4.3	5.6	7.4	6.6	
18.2	19.3	28.6	38.3	30.9	
1	1	1	2	1	
521	474	427.8	650	733	
5000	4442	5000	5000	5000	
125	74.4	88.2	73.4	102	
2018.03.30	2018.05.04	2018.06.27	2018.06.28	2018.07.13	2018.07.27
FU	FU	Cycle2_Screenii	Cycle2_Tx1	Cycle2_Tx2	Cycle2_Tx3
		A0108 D203	A0102 D201	A0106 D104	
19.4	44	49	49	44.1	41.2
6.9	21.3	24.8	24.8	19.2	22.3
30.4	65.3	57	57	41.82	46.64
3	4	4	4	4	4
-	-	1051	1290	982	668
-	-	5000	-	5000	5000
-	-	132	-	135	55.6
2019.05.16	2019.05.17	2019.05.31	2019.06.14	2019.07.05	2019.07.15
Cycle2_Screenii	Cycle2_Tx1	Cycle2_Tx2	Cycle2_Tx3	Cycle2_FU	Cycle2_FU
	A0106 D127	A0106 D127	A0106 D127		
30.2	30.2	33.1	30	28.5	27.6
16.5	16.5	18.4	13.6	11.9	11.9
43.24	43.24	51.62	39.1	38.4	37.72
3	3	3	3	3	3
332	-	362	312	386	258
5000	-	4457	4638	4698	-
31.2	-	39.7	63.6	63.6	-
2019.02.20	2019.02.21	2019.03.08	2019.03.22	2019.04.04	2019.04.19
Cycle2_Screenii	Cycle2_Tx1	Cycle2_Tx2	Cycle2_Tx3	Cycle2_FU	Cycle2_FU
	A0106 D127	A0106 D127	A0106 D127		
42.5	42.5	42	35.5	29	27
16.2	16.2	16.2	12.5	10.2	9.2
32.5	32.5	34.5	29.1	28.5	28.8
3	3	3	3	3	3
97	97	227	170	101	187

2001 0	2001 0	1905 0	1920 0	1880 0	- -
2018.11.02	2019.02.11	2019.03.16	2019.04.03	2019.04.04	2019.04.18
FU	FU	FU	Cycle2_Screenii	Cycle2_Tx1 A0106 D126	Cycle2_Tx2 A0106 D126
-	-	-	63.5	63.5	68.5
23	23	28.3	35.8	35.8	40.4
66.7	55.7	71.4	76.7	76.7	77.9
-	-	-	4	4	4
-	-	-	1386	1303	1518
-	-	-	4867	-	5000
-	-	-	200	-	200

Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22
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2018.08.10 Cycle2_FU	2018.08.24 Cycle2_FU	2018.09.07 Cycle2_FU	2018.09.21 Cycle2_FU	2018.10.05 Cycle2_FU	2018.10.19 Cycle2_FU
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36.3	28.6	27.1	24.2	26.2	27.2
15.9	11.4	9.9	8.9	10.8	10.8
46.36	39.22	30.82	29.44	34.04	33.84
3	3	3	3	3	3
763	819	-	634	-	811
5000	-	-	-	-	5000
108	-	-	-	-	28.2

2019.07.31 Cycle2_FU	2019.08.26 Cycle2_FU	2019.10.16 Cycle2_FU	2020.1.21 FU
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25.4	21.8	19.7	-
10.3	9.8	8.2	5.7
34.68	33.36	27.74	-
3	3	3	-
-	291	287	-
-	-	4625	-
-	-	40.5	-

2019.05.02 Cycle2_FU	2019.05.17 Cycle2_FU	2019.05.31 Cycle2_FU	2019.06.14 Cycle2_FU
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21.8	21.5	17.8	17.4
9.3	8.7	7.3	8
28.46	30.2	31.16	27.48
3	3	3	3
-	197	-	263

-	-	-	2119		
-	-	-	0		
2019.05.02	2019.05.16	2019.05.29	2019.06.21	2019.06.28	2019.08.12
Cycle2_Tx3	Cycle2_Tx4	Cycle2_Tx5	Cycle2_FU	Cycle2_FU	Cycle2_FU
A0106 D126	A0106 D127	A0106 D127			
70.5	59.5	54.5	54	-	50.8
42.4	34.9	28.6	26.8	-	22.4
77.8	72.7	70.4	71.1	-	52.26
4	4	4	4	-	3
1723	1342	1184	758	1058	848
5000	5000	5000	5000	-	-
200	200	200	200	-	-

Visit 23	Visit 24	Visit 25	Visit 26	Visit 27	Visit 28
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2018.12.14	2019.02.12	2019.04.19	2019.06.21	2019.08.16	2019.10.18
FU	FU	FU	FU	FU	FU
24.2	20.6	-	-	-	-
11.9	11.2	10.1	11.6	9.3	11.9
36.74	28.12	-	-	-	-
2	2	-	-	-	-
876	910	-	620	615	614
5000	5000	-	5000	5000	-
105	106	-	78.6	-	-

2019.08.26

Cycle2_FU

47

22.4

53.6

3

857

5000

200

Visit 29	Visit 30
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2019.12.20	2020.02.19
FU	FU
-	-
9.3	8.5
-	-
-	-
-	602
-	5000
-	-

Supplementary table 4. Levels of cytokine biomarkers measured by enzyme-linked imr

Biomarkers	Patient ID.	Cycle	Visit 1	Visit 3
CCL17 (pg/ml)	S001	1st	3503	3262
CCL17 (pg/ml)	S002	1st	1836	1430
CCL17 (pg/ml)	S002	2nd	1324	969
CCL17 (pg/ml)	S003	1st	3796	2619
CCL17 (pg/ml)	S003	2nd	1291	1542
CCL17 (pg/ml)	S004	1st	1459	2674
CCL17 (pg/ml)	S004	2nd	1180	1366
CCL17 (pg/ml)	S005	1st	16782	14449
CCL17 (pg/ml)	S005	2nd	18314	17870
CCL22 (pg/ml)	S001	1st	1592	1997
CCL22 (pg/ml)	S002	1st	5865	6923
CCL22 (pg/ml)	S002	2nd	4644	2290
CCL22 (pg/ml)	S003	1st	14773	14639
CCL22 (pg/ml)	S003	2nd	13583	15787
CCL22 (pg/ml)	S004	1st	2777	3494
CCL22 (pg/ml)	S004	2nd	2166	3084
CCL22 (pg/ml)	S005	1st	3358	2330
CCL22 (pg/ml)	S005	2nd	1154	1085
IL 13 (pg/ml)	S001	1st	188	191
IL 13 (pg/ml)	S002	1st	161	158
IL 13 (pg/ml)	S002	2nd	36	23
IL 13 (pg/ml)	S003	1st	822	747
IL 13 (pg/ml)	S003	2nd	695	742
IL 13 (pg/ml)	S004	1st	79	131
IL 13 (pg/ml)	S004	2nd	82	86
IL 13 (pg/ml)	S005	1st	707	728
IL 13 (pg/ml)	S005	2nd	739	688
IL17 (pg/ml)	S001	1st	333	236
IL17 (pg/ml)	S002	1st	425	329
IL17 (pg/ml)	S002	2nd	197	164
IL17 (pg/ml)	S003	1st	0	0
IL17 (pg/ml)	S003	2nd	0	0
IL17 (pg/ml)	S004	1st	0	0
IL17 (pg/ml)	S004	2nd	0	0
IL17 (pg/ml)	S005	1st	0	0
IL17 (pg/ml)	S005	2nd	0	0
IL 18 (pg/ml)	S001	1st	3430	4004
IL 18 (pg/ml)	S002	1st	5348	3866

IL18 (pg/ml)	S002	2nd	3567	2819
IL18 (pg/ml)	S003	1st	2426	1835
IL18 (pg/ml)	S003	2nd	1629	1637
IL18 (pg/ml)	S004	1st	3050	3044
IL18 (pg/ml)	S004	2nd	2265	2838
IL18 (pg/ml)	S005	1st	2242	2444
IL18 (pg/ml)	S005	2nd	2064	3112
IL22 (pg/ml)	S001	1st	869	940
IL22 (pg/ml)	S002	1st	582	570
IL22 (pg/ml)	S002	2nd	174	75
IL22 (pg/ml)	S003	1st	155	160
IL22 (pg/ml)	S003	2nd	48	55
IL22 (pg/ml)	S004	1st	74	217
IL22 (pg/ml)	S004	2nd	18	30
IL22 (pg/ml)	S005	1st	518	453
IL22 (pg/ml)	S005	2nd	245	259
IgE (kU/L)	S001	1st	17832	11064
IgE (kU/L)	S002	1st	141639	130312
IgE (kU/L)	S002	2nd	77212	78422
IgE (kU/L)	S003	1st	11129	9517
IgE (kU/L)	S003	2nd	7828	6331
IgE (kU/L)	S004	1st	29301	28370
IgE (kU/L)	S004	2nd	22014	24931
IgE (kU/L)	S005	1st	21314	12085
IgE (kU/L)	S005	2nd	7541	9635

nunosorbent assay.

Visit 4	Visit 5	Visit 6	Visit 8	Visit 10
2522	2433	2438	1227	1101
1110	1050	1001	939	939
827	785	636	643	556
3451	2436	1617	1362	2275
1354	1297	588	1476	1536
4849	3786	6491	1683	1873
1408	859	904	1159	820
8783	6011	10604	12703	9684
17555	14128	9323	10293	8856
2072	952	980	442	402
2737	2994	2382	2318	2318
1936	1902	1795	1770	1624
13484	12669	12286	12548	12768
15206	13640	13221	12307	15536
3556	3076	4127	2970	2707
3201	2745	2698	2756	2536
1724	1014	1082	1442	1142
1123	988	925	894	1069
170	159	133	119	92
81	81	63	56	25
22	19	19	18	14
734	678	691	700	715
737	662	635	610	535
88	69	58	72	77
78	89	75	66	44
691	643	676	660	736
701	676	687	677	680
126	119	76	36	77
249	137	128	183	176
158	144	124	139	128
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
2836	2431	2307	1635	1526
3238	2617	2672	2758	3255

2620	2415	2328	1841	2060
2504	2276	2040	1715	1019
2449	1989	1602	1538	1322
2175	3201	3363	2633	2705
3517	3638	2785	3279	3291
608	924	2092	749	2726
1193	809	886	855	487
644	413	159	64	46
209	268	69	95	107
82	74	96	76	39
148	75	68	56	57
52	67	73	59	56
171	152	226	69	120
26	33	19	34	13
599	223	274	239	444
287	135	168	121	105
14923	12085	10157	8010	5778
118280	111065	92940	84192	72759
79512	76814	73151	62677	56796
9682	9875	12399	9312	13001
7997	5498	6400	4663	7021
30677	42127	38687	41200	42840
28147	30584	23737	24960	32034
11238	17196	19299	15163	10921
14989	15782	12507	14440	7665

Visit 11	Visit 12	Visit 13	Visit 14	Visit 15
0	0	114	2	0
418	343			
4772	7448			
382	379	447	440	462
964	806			
912	888			
90	83	72	88	105
19	20			
758	803			
66	53	66	56	45
120	116			
0	0			
1736	1387	1713	1490	1667

1714

1801

443

622

46

35

50

31

46

32

26

96

87

3545

3238

3664

4747

5740

49027

41806

8208

5856

(Emergency Treatment Protocol)

**Clinical Trial for Emergency use Investigating the Efficacy and Safety
of Allogeneic Bone Marrow-derived Mesenchymal Stem Cells for the
Treatment of Moderate-to-Severe Atopic Dermatitis in Adult patient**

Clinical Protocol

Protocol Number :	SCM-CGH-01
Protocol Version :	2.0
Study Drug :	SCM-CGH
Title :	Clinical trial for Emergency use Investigating the Efficacy and Safety of Allogeneic Bone Marrow-derived Mesenchymal Stem Cells for the Treatment of Moderate-to-Severe Atopic dermatitis in Adult patient
Study Phase :	Emergency Use
Study Director :	Jeonghyun Shin, M.D., Ph.D. Department of Dermatology Inha University Hospital College of Medicine, Incheon, South Korea
Study Duration :	Within 24 months from the approval of clinical protocol

▣ Protocol Synopsis

Title	Clinical trial for Emergency use Investigating the Efficacy and Safety of Allogeneic Bone Marrow-derived Mesenchymal Stem Cells for the Treatment of Moderate-to-Severe Atopic dermatitis in Adult patient
Study Site & Director	<ul style="list-style-type: none"> Study Site Department of Dermatology, Inha University Hospital College of Medicine, Incheon, South Korea Study Director Jeonghyun Shin, M.D., Ph.D.
Study Duration	Within 24 months from the approval of clinical protocol
Study Objectives	The objective in this trial is to demonstrate the efficacy and safety of multiple doses of SCM-CGH in adult patient with moderate-to-severe AD
Study Phase and Design	This is a single-center, open-labeled study to evaluate the efficacy and safety of multiple doses of allogeneic mesenchymal stem cells derived from bone marrow in adults with moderate-to-severe atopic dermatitis. The study is 16 weeks (4-week treatment period and 12-week follow-up).
Study Drug	SCM-CGH (allogeneic mesenchymal stem cells derived from bone marrow)
Formulation, Dose and Route of Administration	<ul style="list-style-type: none"> Formulation : allogeneic mesenchymal stem cells derived from bone marrow Dose : 1.0×10^6 cells/kg, every two weeks, a total of 3 infusions Route : intravenous infusion Infusion rate: 2-4.5ml/min Patients weighing less than 50kg, SCM-CGH should be infused slowly over 10 minutes
Study Duration	Total follow-up period for each patient is 12 weeks from the last administration of drug.
Population	Estimated enrollment : 1

Inclusion Criteria	<ul style="list-style-type: none"> - Male and female patients of ages ≥ 20 years and ≤ 60 years - AD patients diagnosed by the criteria of Hannifin and Rajka - Subacute or chronic AD patients that have been present for at least 6 months - Moderate-to-severe AD patients with SCORAD score > 20 - Patients willing to sign the informed consent form
Exclusion Criteria	<ul style="list-style-type: none"> - Symptoms of systemic infection at baseline visit - Asthma at baseline visit - Treatment with systemic steroids, systemic immunosuppressants, or systemic photochemotherapy within 4 weeks before baseline visit - Treatment with topical steroids, oral antibiotics, or topical antibiotics within 2 weeks before baseline visit - Treatment with drugs contraindicated for combination - Pregnant or breast-feeding women or sexually active women of childbearing potential who are unwilling to practice contraception during the study - Treatment with another investigational drug within 30 days before baseline visit - Creatinine $> 2\times$ upper limit of normal (ULN) at screening visit - AST/ALT $> 2\times$ upper limit of normal (ULN) at screening visit - Subjects who had a hypersensitivity to antibiotics or antimycotics - Subjects who had a serious adverse events during stem cell therapy - Any medical or psychiatric condition which, in the opinion of the investigator, would place the patient at risk, interfere with participation in the study, or interfere with the interpretation of study results
Concomitant treatment	<p>Treatment with the following concomitant medication is permitted during study participation</p> <p>① Concomitant medications that the patients have used before the participation in present study are permitted, unless those</p>

	<p>medications do not affect the analysis of efficacy or the safety of study drug.</p> <p>② Symptomatic treatments: emollients not containing corticosteroid, low potent (Group 6~7) topical corticosteroids, antihistamines, or anti-inflammatory drugs</p> <p>③ Temporarily treated medications for the treatment of other diseases or adverse reactions are permitted after the discussion with the clinician.</p> <p>④ All detailed information regarding concomitant treatments (including the treatment for diseases other than AD) will be recorded in CRF.</p>
Prohibited Concomitant Treatment	<p>Treatment with the following medications are prohibited during study participation.</p> <p>① Immunomodulators</p> <p>② High potency (Group 1~5) topical corticosteroids</p> <p>③ Systemic corticosteroids</p> <p>④ Systemic photochemotherapy</p> <p>⑤ Live vaccination</p> <p>⑥ Other treatment considered to affect the immune function</p> <p>When the usage of prohibited concomitant treatments are required to treat patients during the study period upon clinician's decision, those patients will be withdrawn from the clinical study and will be recorded in the last page of case report form (CRF).</p>

Detailed Study Design						
	Visit No.	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Week (+ Day)	Within 4 Weeks	0	2 (± 3)	4 (± 3)	6 (± 3)
	Nomen- clature	Screening visit	Baseline visit	Treatment visit		Midterm visit
	Assessment	Screening Evaluation	Administration	Administration	Administration	Evaluation
	Visit No.	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
	Week (+ Day)	8 (± 3)	10 (± 3)	12 (± 3)	14 (± 3)	16 (± 3)
	Nomen- clature	Mieterm visit				Final visit
	Assessment	Evaluation of efficacy and safety				
Evaluation Criteria	<ul style="list-style-type: none">• Primary efficacy endpoints Mean relative reduction in the severity of AD at 12 weeks after administration of three doses evaluated by EASI, IGA, and SCORAD score• Secondary efficacy endpoints Serum level of biomarkers (IgE, Eonsiophil count, ECP)					
	Adverse reactions, Clinical pathological analysis (hematology, blood chemistry and urine examination), Physical examination, Vital sign					
Tolerability and Safety Assessment						

▣ Study Schedule and Analysis Variables

Period	Screening	Treatment			Follow-up					Closing
Visit	1	2	3	4	5	6	7	8	9	10
Week	Within -4w	0w	2w±3d	4w±3d	6w±3d	8w±3d	10w±3d	12w±3d	14w±3d	16w±3d
Written consent	○									
Pre-treatment medications	○									
Demographic investigation	○									
Medical history	○									
Physical examination	○									○
Vital sign	○	○	○	○	○	○	○	○	○	○
Penicillin skin test	○									
Pregnancy test ¹⁾	○									○
Clinical laboratory test ²⁾	○	○	○	○	○	○		○		○
Chest X-ray	○									○
ECG	○									○
Inclusion/Exclusion	○	○	○	○						
SCORAD, IGA, EASI, BSA	○	○	○	○	○	○	○	○	○	○
Total IgE, ECP	○		○	○	○					○
Biomarker	○		○	○	○	○		○		○
Administration of Drug		○	○	○						
Adverse reactions		○ ³⁾	○	○	○	○	○	○	○	○
Combination drugs		○	○	○	○	○	○	○	○	○

1) Urine HCG examination is performed on women of childbearing potential and the result should be checked before drug administration.

2)

Hematology Hemoglobin, Hematocrit, RBC, WBC, WBC different cell count, Platelet

Blood Chemistry Alkaline phosphatase, BUN, Creatinine, SGPT(ALT), SGOT(AST), Albumin, Total protein, Total bilirubin, Uric acid, Glucose, Cholesterol, Na, K, Cl, Calcium, Phosphorus

Urinalysis: Specific Gravity, Color, pH, Protein, Glucose, Bilirubin, Blood, WBC

3) Biomarker For molecular genetic testing, SST (tube 5mL *3ea, total 15mL) blood is collected at the scheduled visit and delivered to SM Life Science Co., Ltd., the sponsor of the clinical trial. At the 2nd and 3rd IP medication visits (Visit 3, Visit 4), blood is collected before IP medication. As a molecular genetic test, IgG1, IL-4, IL-17, IFN-gamma, IL-6, IL-5, TGF-β1, ICOSL, ACh, IL-13, IL-22, and TARC/CCL-17 are tested.

4) Adverse reactions are assessed for 4 hours after drug administration

Figures

Figure 1

Clinical response of patients with atopic dermatitis to clonal mesenchymal stem cell therapy. (A) Comparison of clinical response between screening and endpoint (followed up at about 16 weeks). The significance of the results was evaluated with Wilcoxon signed-rank test. EASI: Eczema Area and Severity Index, SCORAD: SCORing Atopic Dermatitis, BSA: Body Surface Area, IGA: Investigator Global Assessment. (B) Changes in Eczema Area and Severity Index (EASI) score of atopic dermatitis patients treated with clonal mesenchymal stem cells. ** $p < 0.01$, * $p < 0.05$

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.