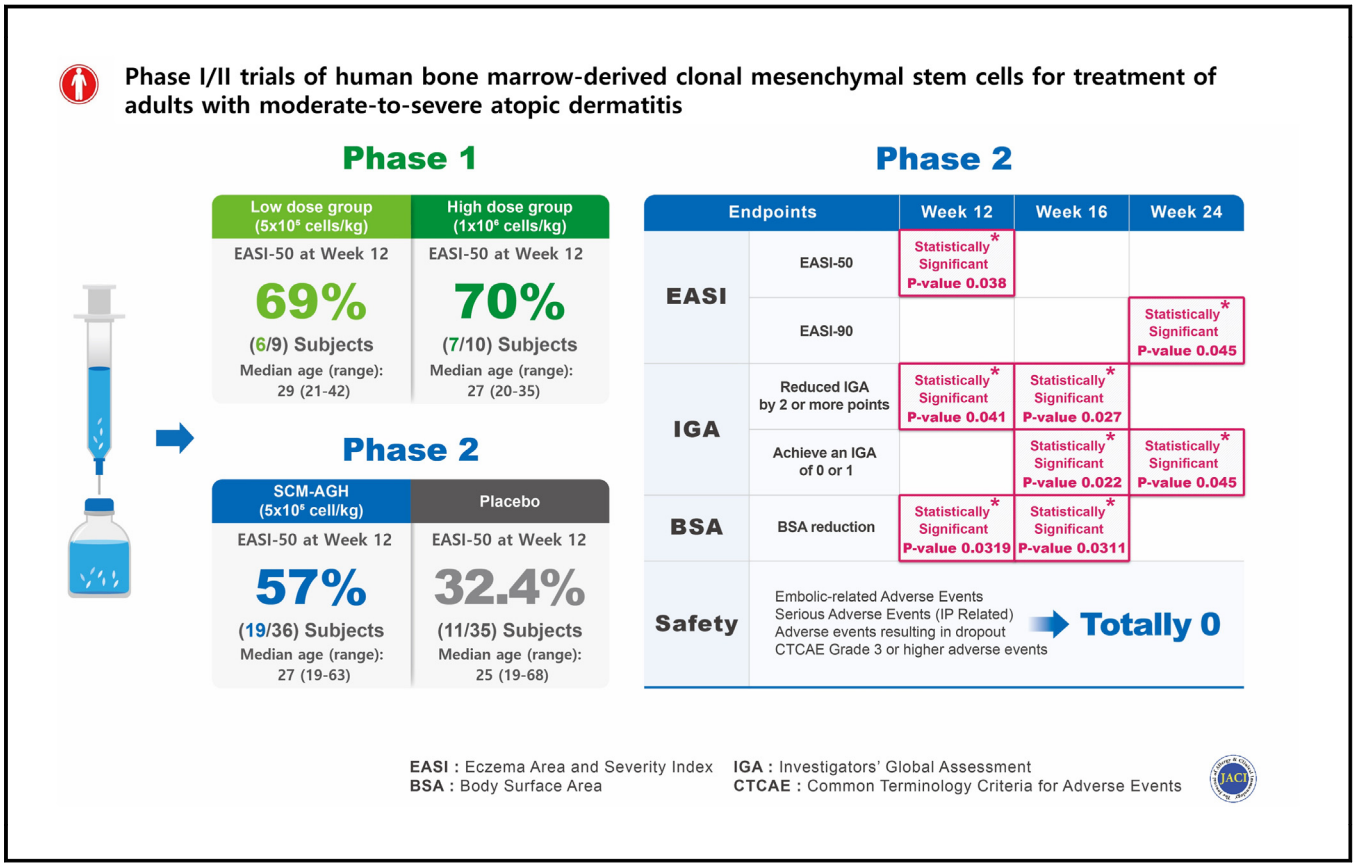
Phase 1/2 trials of human bone marrow–derived clonal mesenchymal stem cells for treatment of adults with moderate to severe atopic dermatitis

Hyun-Min Seo, MD, PhD, Bark-Lynn Lew, MD, PhD, Yang Won Lee, MD, PhD, Sang Wook Son, MD, PhD, Chang Ook Park, MD, PhD, Young Lip Park, MD, PhD, et al

GRAPHICAL ABSTRACT



Capsule summary: Allogeneic human bone marrow–derived clonal mesenchymal stem cells treatment significantly improved symptoms in subjects with moderate to severe atopic dermatitis with a good safety profile.

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Phase 1/2 trials of human bone marrow–derived clonal mesenchymal stem cells for treatment of adults with moderate to severe atopic dermatitis

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Background: Mesenchymal stem cells (MSCs) play important roles in therapeutic applications by regulating immune responses.

Objective: We investigated the safety and efficacy of allogenic human bone marrow–derived clonal MSCs (hcMSCs) in subjects with moderate to severe atopic dermatitis (AD).

Methods: The study included a phase 1 open-label trial followed by a phase 2 randomized, double-blind, placebo-controlled trial that involved 72 subjects with moderate to severe AD.

Results: In phase 1, intravenous administration of hcMSCs at 2 doses (1×10^6 and 5×10^5 cells/kg) was safe and well tolerated in 20 subjects. Because there was no difference between the 2 dosage groups ($P = .9$), it was decided to administer low-dose hcMSCs only for phase 2. In phase 2, subjects receiving 3 weekly intravenous infusions of hcMSCs at 5×10^5 cells/kg showed a higher proportion of an Eczema Area and Severity Index (EASI)-50 response at week 12 compared to the placebo group ($P = .038$). The differences between groups in the Dermatology Life Quality Index and pruritus numeric rating scale scores were not statistically significant. Most adverse events were mild or moderate and resolved by the end of the study period.

Conclusions: The hcMSC treatment resulted in a significantly higher rate of EASI-50 at 12 weeks compared to the control group in subjects with moderate to severe AD. The safety profile of hcMSC treatment was acceptable. Further larger-scale studies are necessary to confirm these preliminary findings. (J Allergy Clin Immunol 2024;154:965-73.)

Key words: *Atopic dermatitis, clinical trial, mesenchymal stem cells, safety, treatment outcome*

Adult human mesenchymal stem cells (MSCs) can be isolated from tissues such as bone marrow, muscle, adipose tissue, and dermis. Although initially believed to be a universal solution for tissue regeneration, MSCs have been found to play important roles in therapeutic applications by regulating immune responses.[1] MSCs can interact with immune cells such as T lymphocytes, B lymphocytes, natural killer cells, monocytes, macrophages, and dendritic cells. They inhibit the release of proinflammatory cytokines and promote the secretion of anti-inflammatory cytokines to regulate immune function.[2]

Atopic dermatitis (AD) is a chronic inflammatory skin disease that begins most frequently in childhood and is characterized by pruritic and recurrent eczematous skin lesions. It is often accompanied by asthma, food allergies, and allergic rhinitis. Over the past few decades, there has been an increase in the prevalence of AD, including adult-onset AD.[3] AD management includes acute flare treatment and maintenance therapy.[4,5] Biologics and small-molecule inhibitors have shown promising efficacy in the treatment of moderate to severe AD. However, ensuring the sustained benefits of these medications requires regular administration, and there remain concerns about the long-term safety of small-molecule inhibitors.[6-8]

Investigations into a range of AD-relevant biochemical pathways associated with immunomodulation resulted in the development of frozen allogenic human bone marrow–derived clonal MSCs (hcMSCs) (SCM-AGH, SCM Lifescience, Seoul, Korea). Previous studies have indicated the potential of hcMSCs for immunomodulation in various conditions. In acute pancreatitis patients, hcMSCs were safe and reduced inflammatory markers.[9] In a preclinical mouse AD model treated with hcMSCs, key biomarkers responsible for regulation of immune inflammatory responses were regulated by hcMSCs.[10] These results suggest that

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Abbreviations used
AD: Atopic dermatitis
AE: Adverse event
BSA: Body surface area
DLQI: Dermatology Life Quality Index
EASI: Eczema Area and Severity Index
hcMSC: Human bone marrow–derived clonal MSC
IGA: Investigator Global Assessment
MSC: Mesenchymal stem cell
TARC: Thymus and activation-regulated chemokine
TEAE: Treatment-emergent AE
Treg: Regulatory T

hcMSCs are effective for modulating the immune inflammatory response in *in vivo* models. Another previous study suggested that umbilical cord–derived MSC extracts ameliorate AD in mice by reducing T-cell responses.[11] In a phase 1/2a human study by Kim et al,[12] human umbilical cord blood–derived MSCs were an effective therapy for patients with moderate to severe AD.

The present study is the first in-human study to assess the safety, tolerability, and efficacy of hcMSCs in subjects with moderate to severe AD. In phase 1, an open-label design was used to define the recommended dose for the subsequent phase 2 study. In phase 2, a randomized, double-blind, placebo-controlled, parallel-arm design was used to evaluate and compare the efficacy of hcMSCs and placebo in subjects with moderate to severe AD.

METHODS

Study design

The study was registered with ClinicalTrials.gov under the identifier NCT04179760. Phase 1 was a randomized, open label, parallel-arm study. Twenty subjects from 6 Korean sites were randomized into 2 parallel arms to receive either high-dose (arm 1, 1×10^6 cells/kg) or low-dose (arm 2, 5×10^5 cells/kg) hcMSCs via 3 intravenous infusions at 2-week intervals. One subject was to be enrolled onto each arm and monitored for safety for 1 week after investigational product administration. If no dose-limiting toxicities were observed in these subjects, an additional 2 subjects were to be enrolled onto each arm and similarly monitored for 1 week after the first investigational product administration. After completion of 1 week of monitoring of each of the initial subjects (6 subjects total), the remainders of each arm (7 subjects per arm, 14 subjects total) were enrolled. After the treatment period, subjects were to visit their study centers for follow-up visits up to 24 weeks (see Fig E1 in this article's Online Repository at www.jacionline.org).

Phase 2 of the study was designed as a multicenter, randomized, double-blind, placebo-controlled, parallel-arm comparison trial. Seventy-two subjects with moderate to severe AD were enrolled from 15 sites in Korea. Because phase 1 showed no dose-dependent difference in the therapeutic efficacy of AD between the groups, phase 2 proceeded with only the low-dose (5×10^5 cells/kg) hcMSCs. After a 4-week screening period, subjects were randomly assigned to receive either hcMSC or placebo. Three weekly intravenous infusions were administered; the total maximum duration of subject participation was 24 weeks. Subjects with intolerable AD symptoms may have received rescue therapy with prohibited medications or nonpharmacologic therapy at the investigator's discretion after discussion with the Contract Research Organization medical monitor and sponsor. In this setting, topical agents would generally have been preferable to systemic rescue treatment. Subjects who received rescue therapy remained in the study and continued with study procedures but did not receive additional study drug administration.

This clinical trial was designed under the strict supervision and communication with the Ministry of Food and Drug Safety of South Korea. The design of phase 1 was primarily focused on participant safety while minimizing the number of patients enrolled to avoid depriving them of other effective treatments due to the uncertain effects of the investigational drug. The chosen doses of 1×10^6 cells/kg and 5×10^5 cells/kg of hcMSCs, tested in an earlier study involving patients with acute pancreatitis, were found to be safe.[9] The study protocol (available in the Online Repository at www.jacionline.org) was approved by all relevant ethics committees and institutional review boards. The trial was conducted according to the principles of the Declaration of Helsinki and the International Council on Harmonization Guidelines for Good Clinical Practice.

Study subjects

Eligible subjects were aged 19 years and older and had a history of AD for at least 1 year; had experienced chronic AD symptoms persistently for a minimum of 6 months; had disease with demonstrated inadequate response to topical medications within the past 6 months; had disease that failed to respond to systemic therapies intended to treat AD within the past 6 months; had an Eczema Area and Severity Index (EASI) score of 16 or higher; had an Investigator Global Assessment (IGA) score of 3 or higher; and had involvement of at least 10% of the total body surface area (BSA) affected by AD. Complete inclusion and exclusion criteria are provided in the study protocol.

Randomization and masking

In phase 1, a total of 20 AD subjects were randomly assigned to receive 2 dose levels of hcMSC (10 subjects received 1×10^6 cells/kg hcMSCs in arm 1 and 10 received 5×10^5 cells/kg in arm 2) at a 1:1 ratio in open-label manner. In phase 2, a total of 72 AD subjects were randomized to receive hcMSCs or placebo at a 1:1 ratio. Masking was not applicable in phase 1 because it was an open-label design. In phase 2, study site personnel, including the investigator and study team, as well as the study subjects remained unaware of the treatment assignment throughout the course of the study. Pharmacy staff (or other qualified site staff) involved with the preparation of the investigational product were unblinded. In the event of a medical emergency requiring medical care, the investigator may have obtained treatment assignment for that subject.

Outcomes

In phase 1, the primary end point was the proportion of subjects who demonstrated an EASI-50 response at week 12 in arm 1 (1×10^6 cells/kg hcMSCs) and arm 2 (5×10^5 cells/kg hcMSCs). In phase 2, the primary end point was the proportion of subjects who demonstrated an EASI-50 response at week 12 in those who received hcMSCs (5×10^5 cells/kg) compared to placebo.

Major secondary end points included the proportion of subjects who received hcMSCs compared to placebo and reached EASI-75 or EASI-90, the proportion of subjects with an IGA score of 0 or 1 during the study period, the proportion of subjects showing a

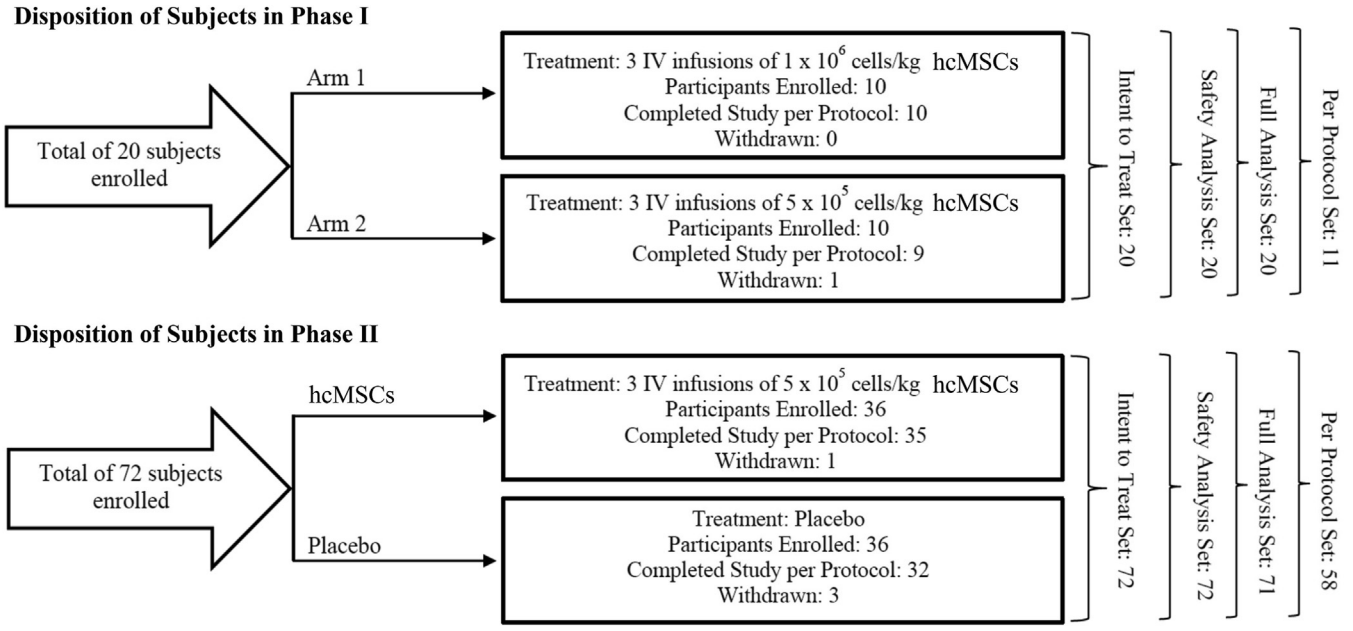

FIG 1. Disposition of subjects in phase 1 and phase 2 studies. *IV,* Intravenous.

decrease in IGA score of 2 points or more, and the proportion of patients showing change from baseline in BSA during the study period. All other prespecified secondary and exploratory outcomes are listed in the study protocol.

Adverse event (AE) reports were collected at each visit. AEs and serious AEs are defined in the study protocol. Treatment-emergent AEs (TEAEs) are defined as AEs that occurred or worsened from the first administration of the study drug up to 28 days after the last dose. If determinations could not be made regarding whether the event was treatment emergent as a result of missing or incomplete data, the AE was treated as treatment emergent. All AEs were coded using the Medical Dictionary for Regulatory Activities (version 24.1).

Rescue therapy

For subjects who were experiencing worsening and intolerable symptoms of AD despite treatment with the investigational product, rescue therapy was permitted. Before rescue, control of AD symptoms should have been attempted by avoiding exacerbating factors, intensifying emollient applications, and using only the permitted study treatments. Use of rescue medications should have been limited to subjects where control of symptoms could not be achieved with increased emollient or low potency and moderate potency of topical corticosteroids or topical calcineurin inhibitors, despite efforts to avoid exacerbating factors and intensifying emollient applications. The use of the rescue therapy was to begin with low potency and moderate potency of topical corticosteroids or topical calcineurin inhibitors, and these rescue medications could commence from the week 4 visit, which was the last dose of investigational product. High- and ultra-high–potency topical corticosteroids and systemic therapies could be considered thereafter according to the investigator's medical assessment if low and moderate administration of topical corticosteroids or topical calcineurin inhibitors did not provide relief to subjects. Using oral corticosteroid as the standard of care for AD was not permitted. In the case of worsening of AD symptoms, subjects who received systemic rescue therapy were to remain in the study and continue with study procedures but would not continue to receive the study drug. The investigator's discretion was to be used to determine whether it was possible to delay systemic rescue therapy until 2 weeks from the last dose of the investigational product (until visit 5). The investigator should have considered whether any rescue therapy should be stopped before the week 12 visit to facilitate the efficacy assessment, but if the subject's AD status was still intolerable, rescue therapy could have been continued. The administration of rescue medication was not considered a prohibited medication or a protocol deviation.

Statistical analyses

Data were collected following the study protocol. All efficacy parameters were analyzed descriptively with the primary analysis confirmed using the full analysis set and supported by the per-protocol set. Continuous variables were presented with their mean values along with either standard deviation or range of values. The number and percentage of subjects reaching categorical end points were categorized by groups. The primary end point and selected secondary categorical end points were analyzed by chi-square tests at the 5% level of significance. For analyses of primary and secondary efficacy end points in the full analysis set population, the last observation carried forward (aka LOCF) method was adopted to establish the missing value if a subject did not attend a scheduled clinic visit or did not undergo the scheduled assessments. No imputation method was performed to estimate missing values for safety variables and efficacy end points that were analyzed in the per-protocol population.

Data availability statement

Data sets, including the study protocol, statistical analysis plan, and individual patient data, will be made available within three

TABLE I. Baseline subject demographic and clinical characteristics

	Phase 1		Phase 2	
Characteristic	**Arm 1 (1×10^6 cells/kg hcMSCs) (n = 10)**	**Arm 2 (5×10^5 cells/kg hcMSCs) (n = 10)**	**5×10^5 cells/kg hcMSCs (n = 36)**	**Placebo (n = 36)**
Age (years) median (range)	29 (21-42)	27 (20-35)	27 (19-63)	25 (19-68)
Male sex, no. (%)	9 (90)	9 (90)	24 (67)	26 (72)
Body mass index (kg/m^2), mean ± SD	27.7 ± 3.3	23.7 ± 4.3	25.6 ± 5.4	25.1 ± 5.5
EASI score, mean ± SD	28.4 ± 15.2	25.7 ± 8.2	23.7 ± 6.8	22.9 ± 7.6
IGA score, no. (%)				
Moderate (grade 3)	5 (50)	6 (60)	26 (72)	28 (78)
Severe (grade 4)	5 (50)	4 (40)	10 (28)	8 (22)
BSA affected (%), mean ± SD	44 ± 21	44 ± 12	38 ± 15	34 ± 13
Pruritus NRS score, mean ± SD				
24 hours (average)	NA	NA	7 ± 2	7 ± 2
24 hours (peak)	NA	NA	8 ± 2	8 ± 2
DLQI, mean ± SD	NA	NA	15 ± 6	15 ± 7

NA, Not applicable; *NRS,* numeric rating scale.

TABLE II. Primary and secondary end points

	Phase 1		Phase 2	
Primary end point	**Arm 1 (n = 10)**	**Arm 2 (n = 10)**	**hcMSCs (n = 36)**	**Placebo (n = 35)**
EASI-50 at week 12†	7 (70%)	6 (67%)	19/33 (58%)*	11/34 (32%)

Secondary end point	**5×10^5 cells/kg hcMSCs (n = 36)**	**Placebo (n = 35)**	***P* value**
EASI-75			
Week 12	6/33 (18%)	2/34 (6%)	.1
Week 16	9/34 (27%)	4/33 (12%)	.4
Week 20	12/34 (35%)	5/31 (16%)	.079
Week 24	13/34 (38%)	6/33 (18%)	.069
EASI-90			
Week 12	4/33 (12%)	2/34 (6%)	.4
Week 16	4/34 (12%)	1/33 (3%)	.2
Week 20	6/34 (18%)	2/31 (6%)	.2
Week 24	8/34 (24%)*	2/33 (6%)	.045*
IGA score decreased by ≥2 points			
Week 12	6/33 (18%)*	1/34 (3%)	.041*
Week 16	7/34 (21%)*	1/33 (3%)	.027*
Week 20	7/34 (21%)	4/31 (13%)	.4
Week 24	9/34 (26%)	3/33 (9%)	.1
IGA score of 0 or 1			
Week 12	3/33 (9%)	0/34	.1
Week 16	5/34 (15%)*	0/33	.022*
Week 20	6/34 (18%)	2/31 (6%)	.7
Week 24	8/34 (24%)*	2/33 (6%)	.045*
BSA % score from baseline			
Week 4	−14 ± 53	−10 ± 33	.7
Week 8	−33 ± 34	−21 ± 36	.2
Week 12	−37 ± 35*	−19 ± 36	.032*
Week 16	−45 ± 33*	−27 ± 35	.031*

*$P < .05$ compared to placebo.
†Primary end point.

months of the initial request to researchers who submit a methodologically sound proposal. Data will be made available after de-identification in accordance with applicable privacy laws, data protection regulations, and consent and anonymization requirements.

RESULTS

Study subjects

An overview of the disposition of study subjects in phase 1/2 is presented in Fig 1. During phase 1 of the study, 20 subjects were enrolled. Nineteen of these participants (95%) completed the

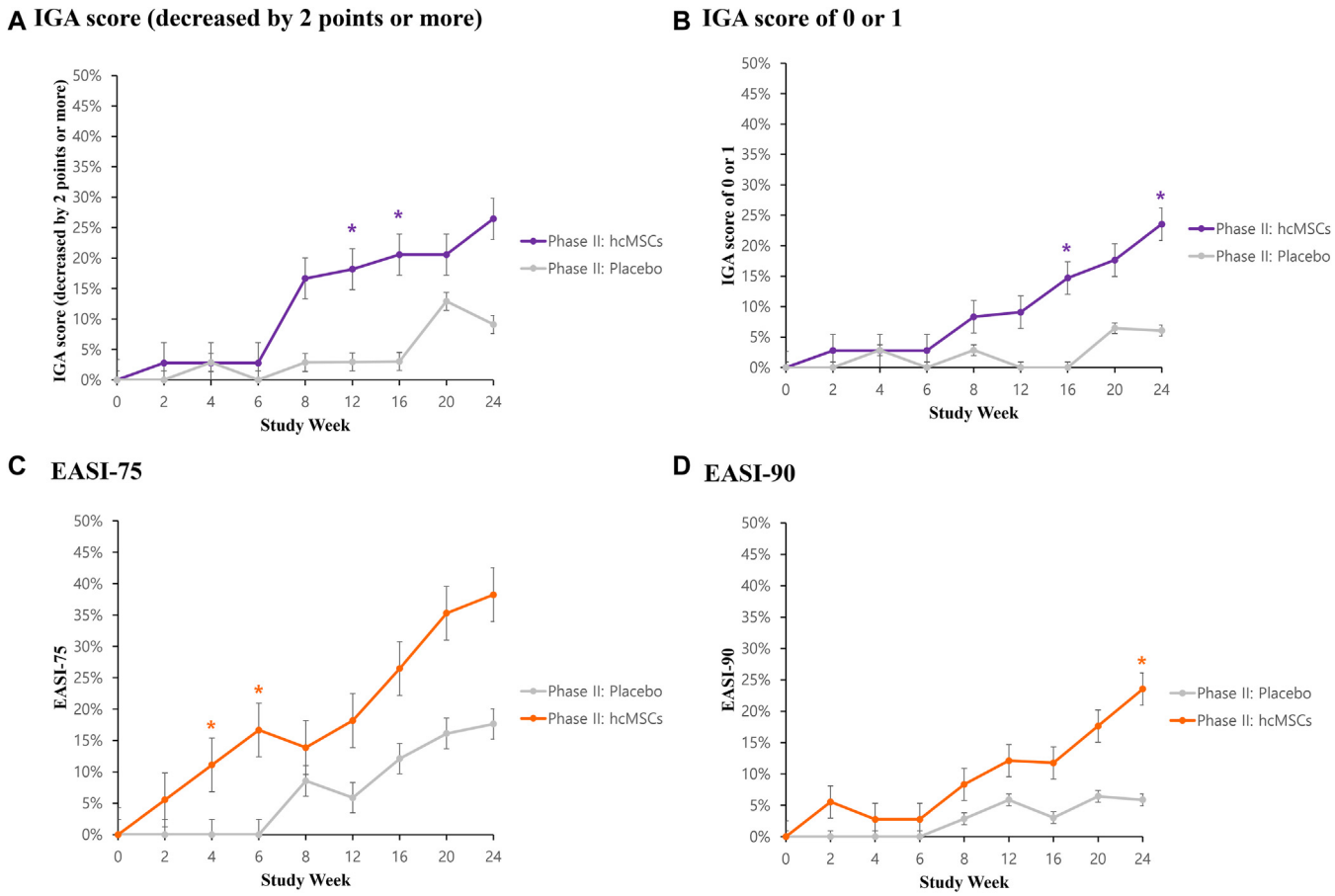

FIG 2. Key secondary end points in phase 2. Proportion of subjects **(A)** with IGA score decreased by 2 points or more or **(B)** with IGA scores of 0 or 1 was higher in hcMSC group compared to placebo group. **(C)** Proportion of subjects with EASI-75 significantly increased in hcMSC group, showing rapid improvement compared to placebo group at week 4. **(D)** EASI-90 showed significant difference between hcMSC group and placebo group at week 24. *$P < .05$.

study following the protocol. During phase 2, a total of 84 subjects were initially screened; of these, 72 were enrolled onto the study after 12 subjects were removed because they did not meet the inclusion criteria. A total of 67 subjects completed the study. Baseline demographics and clinical characteristics were balanced across groups (Table I).

Primary end point

In phase 1 of the study, the proportion of subjects with an EASI-50 response was 70% in arm 1 (1×10^6 cells/kg hcMSCs) and 67% in arm 2 (5×10^5 cells/kg hcMSCs) at week 12; there was no significant difference between the 2 groups ($P = .9$). In phase 2 of the study, the proportion of subjects with an EASI-50 response was greater, with 5×10^5 cells/kg hcMSCs (58%) compared to placebo (32%) at week 12 ($P = .038$) (Table II).

Secondary end points

In phase 2 of the study, the proportion of subjects with an EASI-90 response was greater with 5×10^5 cells/kg hcMSCs (24%) compared to placebo (6%) at week 24 ($P = .045$). The subjects receiving 5×10^5 cells/kg hcMSCs quickly attained EASI-75 and showed a statistically significant difference compared to the placebo at week 4 (11% vs 0) [difference (95% confidence interval) 11% (1-21); $P = .045$] and week 6 (17% vs 0) [17% (4-29); $P = .012$]. An IGA score of 0/1 was recorded by 15% versus 0 [15% (3-27); $P = .022$] at week 16 and by 24% versus 6% [18% (1-34); $P = .045$] at week 24 for 5×10^5 cells/kg hcMSCs and placebo, respectively. An IGA score that decreased by 2 points or more occurred in 18% versus 3% [15% (1-30); $P = .041$] at week 12 and 21% versus 3% [18% (3-32); $P = .027$] at week 16 for 5×10^5 cells/kg hcMSC and placebo, respectively. Change in total BSA from baseline was greater with 5×10^5 cells/kg hcMSCs compared to placebo at week 12 (-37 ± 35 vs -19 ± 36, $P = .032$) and week 16 (-45 ± 33 vs -27 ± 35, $P = .031$). For other secondary outcomes, the differences were not statistically significant between groups (Table II and Fig 2). In the phase 2 study, changes in pruritus numeric rating scale scores at 12 weeks were -2.2 ± 2.1 in the hcMSCs group and -1.8 ± 2.4 in the control group. At 24 weeks, the scores were -2.1 ± 2.2 in the hcMSCs group and -2.0 ± 2.3 in the control group. There was no statistically significant difference between the groups at either time point. For the Dermatology Life Quality Index (DLQI), reductions at 12 weeks were -6.2 ± 6.1 in the hcMSCs group and -5.0 ± 6.2 in the control group. At 24 weeks, reductions were -6.8 ± 7.9 in the hcMSCs group and -4.5 ± 7.1 in the control group. These differences were

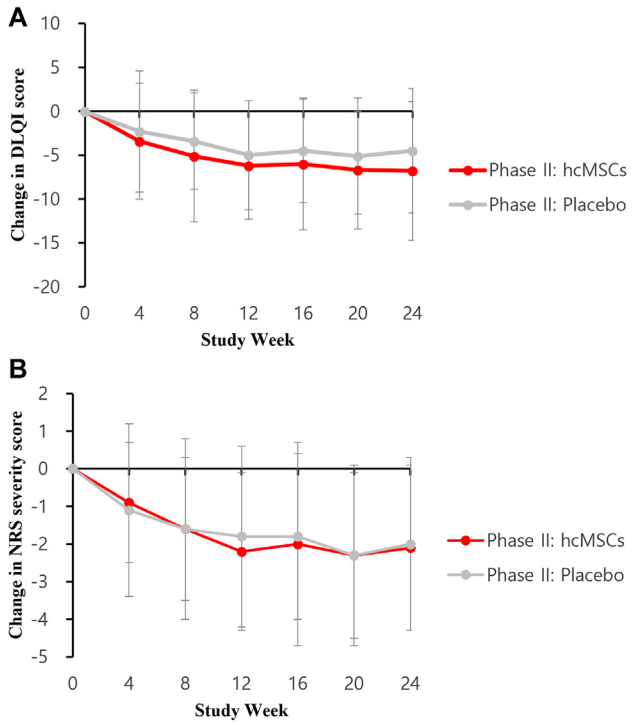

FIG 3. Effectiveness of hcMSC treatment on **(A)** DLQI and **(B)** pruritus numeric rating scale (NRS) scores in phase 2.

not statistically significant (Fig 3). Changes in serum thymus and activation-regulated chemokine (TARC), IL-17, and IL-22 levels showed no significant differences between the groups. Notably, IL-17 was not detectable in any participant from the placebo group, resulting in consistent zero scores across this group (Fig 4).

Safety

In phase 1, 10% (1/10) and 30% (3/10) of subjects experienced AEs in arm 1 and arm 2, respectively. In phase 2, 28% (10/36) and 22% (8/36) of subjects in the hcMSCs and placebo groups, respectively, experienced AEs. Most AEs was nonserious and mild or moderate in severity, with most resolved or resolving by the end of the study period (Table III). The most common TEAEs by system organ class were infections and infestations, which occurred in 2 (10%) of 20 subjects in phase 1 and 4 (6%) of 72 subjects in phase 2. By the preferred term, the TEAE in arm 1 was herpes ophthalmic, and that in arm 2 was gingivitis in phase 1. In phase 2, the TEAEs in the 5×10^5 cells/kg hcMSC group were impetigo and upper respiratory tract infection, and those in the placebo group were nasopharyngitis and paronychia (see Table E1 in this article's Online Repository at www.jacionline.org).

DISCUSSION

This study was conducted to investigate the safety and efficacy of hcMSCs for treatment of patients with moderate to severe AD. Phase 1 was a randomized, open-label, parallel-arm study of 20 subjects. Treatment with hcMSCs at both doses (1×10^6 cells/kg and 5×10^5 cells/kg) was well tolerated. Phase 2 was a multicenter, randomized, double-blind, placebo-controlled, parallel-arm study of 72 subjects. At week 12, the administration of 3

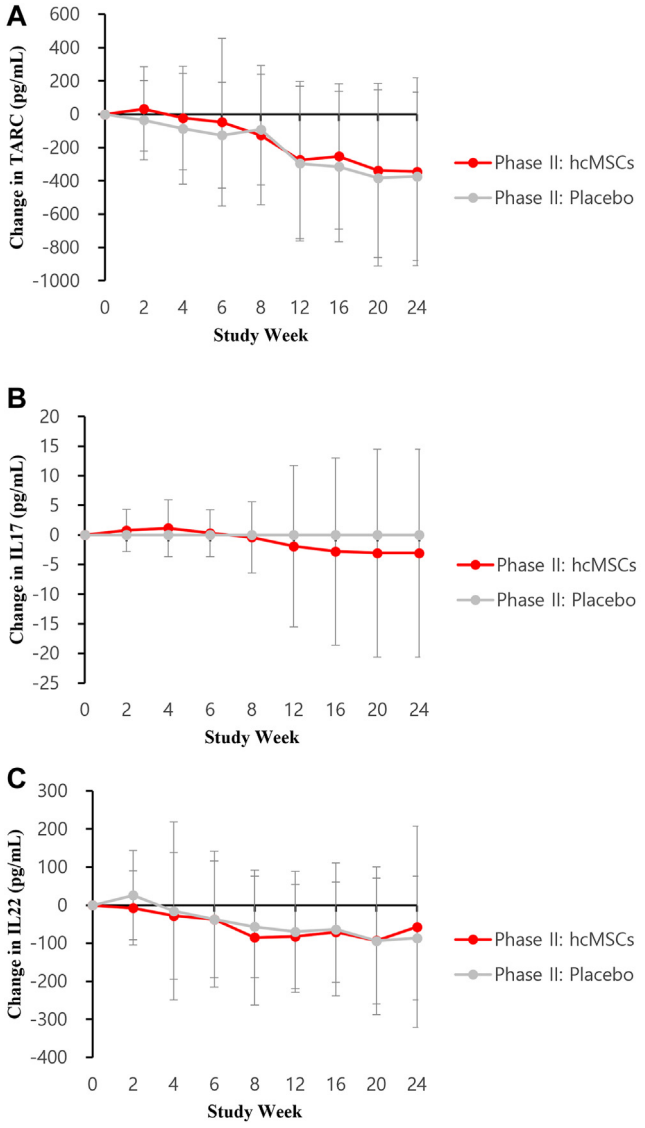

FIG 4. Changes in **(A)** TARC, **(B)** IL-17, and **(C)** IL-22 levels during phase 2.

intravenous infusions of 5×10^5 cells/kg hcMSCs every 2 weeks resulted in a significantly higher proportion of subjects with an EASI-50 response compared to the placebo group.

MSCs can regulate lymphocyte proliferation and function. A recent study in an AD-like mouse model showed that MSCs effectively suppressed the activity of the JAK-STAT pathway and the expression of receptors for IL-4, IL-13, IL-17, and IgE.[13] In addition, the immunomodulatory functions of MSCs involve regulatory T (Treg) cells characterized by $CD4^+CD25^+FoxP3^+$ expression, which negatively regulate inflammatory responses.[14] FoxP3-expressing Treg cells, found within the subset of $CD4^+CD25^+$ T cells, play crucial roles in suppressing deleterious immune responses and inflammation by inhibiting $CD4^+$ T cells, $CD8^+$ T cells, dendritic cells, natural killer cells, and B cells.[15] A previous study of hcMSCs found evidence that ICOSL, a glycosylated transmembrane structure, expression in human MSCs, plays an important role in contact-dependent regulation of MSC-mediated Treg cell induction.[14] The findings to date

TABLE III. Summary of TEAEs

Characteristic	Phase 1		Phase 2	
	Arm 1 (n = 10)	Arm 2 (n = 10)	hcMSCs (n = 36)	Placebo (n = 36)
Any TEAE	1 (10)	3 (30)	10 (28)	8 (22)
Any of the following TEAE (worst grade experienced)				
Mild (grade 1)	1 (10)	2 (20)	6 (17)	5 (14)
Moderate (grade 2)	0	1 (10)	5 (14)	5 (14)
Serious TEAEs	0	0	0	0
Outcome of TEAEs				
Recovered/resolved	1 (10)	2 (20)	8 (22)	8 (22)
Not recovered/not resolved	0	1 (10)	2 (6)	0
Action taken				
No change to study treatment	1 (10)	3 (30)	10 (28)	8 (22)
Congenital anomaly/birth defect TEAEs	0	0	0	0
TEAEs leading to persistent or significant disability or incapacity	0	0	0	0
TEAEs leading to death	0	0	0	0
TEAEs leading to inpatient hospitalization or prolongation of existing hospitalization	0	0	0	0
Life-threatening TEAEs	0	0	0	0
TEAEs associated with other serious or important medical events	0	0	0	0
TEAEs involving cancer	0	0	0	0
TEAEs involve overdose	0	0	0	0
Study drug relationship to TEAEs (%)				
Unrelated or unlikely related	1 (10)	3 (30)	8 (22)	5 (14)
Unlikely related	0	0	3 (8)	2 (6)
Possibly related	0	0	0	2 (6)
Probably related	0	0	1 (3)	0
Definitely related	0	0	0	0

Data are presented as nos. (%). TEAEs were defined as AEs that occurred or worsened from first administration of study drug up to 28 days after last dose. If subject experienced same AE multiple times, it was only counted once.

indicate that MSC therapy could modulate the abnormal immune and inflammatory responses observed in AD.

The results of a previous study involving patients with acute pancreatitis demonstrated the safety and tolerability of intravenous administration of hcMSCs, with no AEs related to the study drug reported.[9] In the present phase 1 study, 4 TEAEs were reported. Among these TEAEs, 3 were classified as grade 1 (mild) and 1 as grade 2 (moderate) in severity. All TEAEs were transient and resolved, except for a case of alopecia areata that persisted at the time of study completion. Regarding safety findings in phase 2, TEAEs were reported in 18 of 72 subjects, all classified as grade 1 (mild) or grade 2 (moderate). No grade 3 or higher TEAEs were reported for any subject. All TEAEs were transient and resolved by the end of the study. Overall, treatment with hcMSCs was safe and well tolerated by subjects with moderate to severe AD.

Among patients who did not experience EASI-50, EASI-75, or EASI-90 at week 12, there was continued improvement over time after 3 intravenous infusions of hcMSCs administered every 2 weeks. In phase 2 of the study, the proportion of subjects with an EASI-90 response was greater with 5×10^5 cells/kg hcMSCs (24%) compared to placebo (6%) at week 24 ($P = .045$). This suggests that the immunomodulating effect induced by hcMSCs is sustained over a prolonged period.

This study had a few limitations. First, despite being a randomized, double-blind, multicenter, placebo-controlled study, the number of patients with moderate to severe AD was limited, resulting in reduced statistical power. Second, rescue medication provided to study subjects could have affected the efficacy outcomes for EASI-50 at week 12. In phase 1, 45% of all subjects received rescue therapy. In phase 2, the hcMSC and placebo groups received rescue therapy at similar rates: 61% and 64%, respectively. In additional analyses conducted to exclude the influence of rescue therapy, the proportion of subjects without rescue therapy with an EASI-50 response at 12 weeks was 54% (13/24) in the hcMSCs group and 26% (6/23) in the placebo group ($P < .05$). Third, although the EASI scores showed statistically significant results, the DLQI, pruritus numeric rating scale scores as well as laboratory findings including TARC, IL-17, and IL-22 did not reveal any significant differences between groups. This indicates that additional analysis and comparison will be required with a sufficient sample size in future studies.

In conclusion, our findings provide preliminary evidence that hcMSC treatment is associated with significant improvements in AD symptoms. The safety and tolerability profile of hcMSC treatment is acceptable. A larger-scale study is necessary to conduct a more comprehensive evaluation of the efficacy of hcMSCs in patients with moderate to severe AD and to determine the long-term sustainability of the observed effects.

DISCLOSURE STATEMENT

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Key messages

- **This phase 1/2 study examined the safety, tolerability, and efficacy of allogenic hcMSCs in patients with moderate to severe AD.**
- **Treatment significantly improved symptoms in subjects with moderate to severe AD.**

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