Exosome-Based Topical Therapy for Facial Atopic Dermatitis

Jovian Wan, MBChB, Song Eun Yoon, MD,† Jong-Keun Song, MD,‡ Isaac Kai Jie Wong, MD,§ Jin-Hyun Kim, MD,‖ and Kyu-Ho Yi, MD, PhD‖¶*

Background: Atopic dermatitis (AD) is a chronic inflammatory skin condition that significantly impairs quality of life. Current therapies, including corticosteroids and calcineurin inhibitors, often provide incomplete relief or have undesirable side effects. Exosome-based therapies derived from adipose-derived mesenchymal stem cells (ADMSCs) offer a novel, multifaceted approach to addressing inflammation, skin barrier dysfunction, and pruritus, presenting a promising alternative for AD management.

Objective: This case series evaluates the efficacy and safety of ADMSC-derived exosome-based topical formulations (ZISHEL XOMAGE; Zishel Bio Inc., Seoul, Korea), in improving clinical and barrier-related outcomes in patients with moderate-to-severe facial AD.

Methods: Twenty adults with moderate-to-severe facial AD (vIGA-AD scores 3–4) applied ADMSC-derived exosome twice daily for 6 weeks. Clinical assessments included vIGA-AD scores, transepidermal water loss (TEWL), and corneometry for hydration. Two blinded dermatologists independently assessed outcomes. Before-and-after photographs were taken under standardised conditions. Pruritus severity was evaluated using a visual analogue scale (VAS).

Results: Eighty-five percent of patients achieved at least a 1-point reduction in vIGA-AD scores, with 50% achieving a 2-point reduction. Corneometry indicated a 58% improvement in hydration, while TEWL measurements demonstrated a 42% reduction, reflecting enhanced barrier integrity. Pruritus VAS scores declined by 70%. No adverse events were reported, and inter-rater reliability for vIGA-AD assessments was high (Cohen kappa = 0.84). Representative cases highlighted substantial improvements in erythema, lichenification, and skin texture.

Conclusion: ADMSC-derived exosome products showed significant efficacy in reducing AD severity and restoring barrier function, with excellent safety profiles. Larger, randomised controlled trials with extended follow-up are recommended to confirm these findings and establish these products as viable treatment options for AD.

Key Words: Adipose-derived mesenchymal stem cells, atopic dermatitis, exosomes, transepidermal water loss

(*J Craniofac Surg* ;00: 000–000)

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterised by erythema, pruritus, and compromised skin barrier function.[1] The prevalence of AD has been rising globally, particularly in developed countries, with estimates suggesting that up to 20% of children and 3% of adults are affected.[2] This increasing prevalence is likely a result of complex interactions between genetic factors and environmental influences, including urbanisation, climate change, pollution, and changes in diet. In urban areas, for example, increased exposure to pollutants, such as tobacco smoke, diesel fumes, and particulate matter, has been linked to a higher risk of developing AD. In addition, lifestyle changes such as reduced exposure to sunlight, changes in diet, and the overuse of antibiotics are believed to play a role in the disease's rising incidence. Despite the increasing prevalence and the availability of a range of treatments, many individuals continue to struggle with persistent symptoms and frequent flare-ups, highlighting the limitations of existing therapies.[3] Conventional treatments for AD typically focus on controlling inflammation, alleviating pruritus, and restoring skin barrier function. Topical corticosteroids and calcineurin inhibitors (eg, tacrolimus and pimecrolimus) are the mainstays of therapy; however, their prolonged use can lead to side effects, such as skin thinning, increased risk of infections, and potential systemic absorption.[1,4,5] In addition, corticosteroid-induced skin atrophy, particularly when used on sensitive areas like the face, is a common concern. Consequently, these therapies are often avoided or limited, especially in pediatric patients or individuals with sensitive skin.[6,7] Therefore, there remains a significant need for innovative and safer therapeutic alternatives that can address the underlying pathophysiology of AD while offering long-term relief and minimal side effects.

In recent years, the field of stem cell-based therapies has garnered significant attention due to the regenerative and immunomodulatory properties of mesenchymal stem cells (MSCs). These cells have been shown to have the ability to modulate immune responses, repair damaged tissues, and restore normal tissue function. MSCs, which can be derived from various sources such as bone marrow, adipose tissue, and umbilical cord blood, exert their effects through the secretion of bioactive molecules in the form of extracellular vesicles, particularly exosomes.[8] Exosomes are small membrane-bound vesicles ranging in size from 30 to 150 nm and are involved in cell-to-cell communication by transferring a variety of biomolecules, including proteins, lipids, and nucleic acids. This mechanism of

From the *Medical Research Inc., Wonju, Korea; †BRANDNEW Aesthetic Surgery Clinic; ‡Pixelab Plastic Surgery Clinic, Seoul, korea; §The Artisan Clinic, Singapore; ‖You and I Clinic, Seoul, Korea; and ¶Department of Oral Biology, Division of Anatomy and Developmental Biology, Human Identification Research Institute, BK21 FOUR Project, Yonsei University College of Dentistry, Seodaemun-gu, Seoul, Korea.

Received March 12, 2025.

Accepted for publication March 24, 2025.

Address correspondence and reprint requests to Kyu-Ho Yi, MD, Department of Oral Biology, Division of Anatomy and Developmental Biology, Human Identification Research Institute, BK21 FOUR Project, Yonsei University College of Dentistry, Seoul, South Korea; E-mail: kyuho90@daum.net

J.W. and K.-H.Y.: conceptualization. J.W.: writing-original draft preparation. J.W., S.E.Y., J.K.S., I.K.J.W., J.-H.K., and K.-H.Y.: writing-review and editing. J.W. and K.-H.Y.: visualization. K.-H.Y.: supervision. All authors have reviewed and approved the article for submission.

The authors report no conflicts of interest. This study was conducted in compliance with the principles set forth in the Declaration of Helsinki.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.jcraniofacialsurgery.com.

ISSN: 1536-3732

DOI: 10.1097/SCS.0000000000011459

intercellular communication has made exosomes an exciting therapeutic tool, particularly for conditions like AD, where inflammation and immune dysregulation play pivotal roles. Exosomes have demonstrated potential to modulate immune responses, reduce inflammation, and even repair damaged skin cells, making them a promising therapeutic option for AD and other inflammatory diseases. They offer a novel means of delivering therapeutic agents directly to target cells without the risks associated with other treatments. Their small size and membrane-bound nature facilitate better tissue penetration and more efficient delivery, especially in inflamed and damaged tissues such as those found in AD.[9,10]

Adipose-derived mesenchymal stem cells (ADMSCs) are particularly advantageous due to their accessibility, ease of harvesting, and ability to yield a high quantity of exosomes. ADMSC-derived exosomes (ADMSCs-EXOs) have been shown to have anti-inflammatory, immunomodulatory, and skin barrier-repairing effects, making them a promising candidate for the treatment of AD.[11,12] Furthermore, because exosomes are noncellular, they pose minimal risks of immune rejection, tumourigenesis, and other safety concerns that can arise with cell-based therapies. As a result, exosome-based therapies have the potential to offer a novel, noninvasive, and safer approach to managing AD, particularly in cases where conventional treatments have proven insufficient. These advantages make exosome-based therapies an attractive alternative for patients who require long-term management of their condition, as they offer a targeted, effective, and low-risk treatment option. Unlike traditional therapies, which may require ongoing or repeated use with potential side effects, exosome treatments could offer longer-lasting relief from the underlying causes of AD, such as immune dysregulation and skin barrier dysfunction.[13,14]

This study aims to evaluate the clinical efficacy and safety of ADMSC-derived exosome formulations (ZISHEL XOMAGE, Zishel Bio Inc., Seoul, Korea) marketed and used as a cosmetic product in accordance with regulatory guidelines, in adult patients with moderate-to-severe facial AD. By contributing to the growing body of evidence on exosome-based topical therapies, this research provides valuable insights into their clinical potential through clinical observations and patient-reported outcomes.

METHODS

This prospective case series was conducted at a single dermatology clinic in Seoul, Korea, with the aim of evaluating the clinical outcomes of topical ADMSC-derived exosome (ZISHEL XOMAGE, Zishel Bio Inc., Seoul, Korea) in patients with moderate-to-severe AD localized to the face. A total of 20 adult patients, aged 18 to 55 years, were included in the study. All patients met the following inclusion criteria: a diagnosis of moderate-to-severe AD affecting the facial region, as defined by a validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of 3 (moderate) or 4 (severe), and the presence of erythema, excoriation, lichenification, and pruritus on the face.[15,16] Patients with a history of systemic immunosuppressive therapy within 4 weeks before enrollment, those with known allergies to exosome components or other ingredients in the formulations, or those with other significant skin diseases were excluded from the study.

Patients applied ZISHEL XOMAGE (Zishel Bio Inc., Seoul, Korea) topically twice daily for 6 weeks. Patients were instructed to apply the product to the affected areas of the face, avoiding sensitive areas such as the eyes. Clinical assessments were made at baseline, and weekly follow-up visits were conducted throughout the 6-week treatment period. The primary outcomes were clinical improvement, as assessed by changes in vIGA-AD scores, skin hydration, as measured by corneometry, and epidermal barrier function, as assessed by transepidermal water loss (TEWL).[17] Secondary outcomes included pruritus severity, as measured by the visual analog scale (VAS), and biomarker analysis of skin biopsies for key epidermal proteins involved in skin barrier function.

Clinical Assessments

The vIGA-AD scale was used to assess the severity of AD at baseline and during follow-up visits. The scale evaluates 5 key features of AD: erythema (redness), oedema (swelling), papulation (raised bumps), excoriation (scratches), and lichenification (thickened skin). Each feature is rated on a scale from 0 to 4, with 0 representing no involvement and 4 representing severe involvement. The total vIGA-AD score ranges from 0 to 20, with higher scores indicating more severe disease.

Skin hydration was measured using corneometry (Corneometer CM 825, Courage+Khazaka electronic GmbH, Cologne, Germany), a noninvasive technique that quantifies the moisture content of the skin by measuring the dielectric constant of the stratum corneum.[17] A higher dielectric constant indicates greater skin hydration. TEWL, another key indicator of skin barrier function, was assessed using Tewameter TM 300 (Courage+Khazaka electronic GmbH, Cologne, Germany), which measures the amount of water vapor lost from the skin surface.[18] A lower TEWL value indicates better skin barrier function. Pruritus severity was assessed using the VAS, where patients rated the intensity of their itch on a scale from 0 (no pruritus) to 10 (worst possible pruritus).

Safety and Tolerability

The safety and tolerability of the treatments were monitored throughout the study. Patients were asked to report any adverse events, such as irritation, erythema, stinging, or hypersensitivity reactions, which were recorded and analysed for their frequency and severity.

RESULTS

Clinical Outcomes

After 6 weeks of treatment with ZISHEL XOMAGE (Zishel Bio Inc., Seoul, Korea), significant clinical improvements were observed in the majority of patients (Figs. 1, 2). Eighty-five percent of patients experienced at least a 1-point reduction in their vIGA-AD score, indicating a clinically meaningful improvement. Half of the cohort (50%) achieved a 2-point reduction in vIGA-AD, which corresponds to a significant improvement in disease severity. The overall median reduction in vIGA-AD scores was 2 points, suggesting that these exosome-based formulations had a notable effect on reducing the severity of AD symptoms (Table 1, Supplemental Digital Content 1, http://links.lww.com/SCS/H822).

Skin Hydration and Barrier Function

Skin hydration, as measured by corneometry, increased by an average of 58% ($P < 0.01$) following 6 weeks of treatment. This result indicates that the topical application of ZISHEL XOMAGE (Zishel Bio Inc., Seoul, Korea) led to a substantial improvement in skin moisture content, which is typically impaired in patients with AD. TEWL measurements showed a 42% reduction ($P < 0.01$), further suggesting that the exosome-

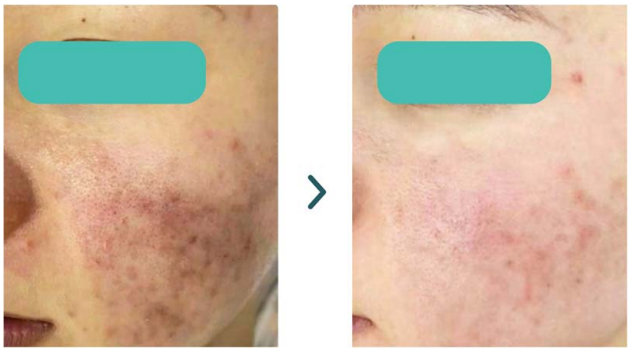

FIGURE 1. Baseline and week 6 photographs of patient A demonstrating reduction in erythema and pruritus after treatment with ADMSC-derived exosome (ZISHEL XOMAGE, Zishel Bio Inc., Seoul, Korea).

based products helped restore the integrity of the skin barrier by reducing water loss.

Pruritus Severity

Pruritus, one of the most distressing symptoms of AD, showed a marked improvement in patients who received the exosome-based treatment. On the VAS, patients reported a 70% reduction in pruritus severity, with the average baseline score of 7.8 decreasing to 2.3 by the end of the study. This reduction in itch severity is consistent with the observed reduction in inflammation and clinical severity, further supporting the potential of exosome-based therapies to alleviate the itch-scratch cycle that perpetuates AD.

Safety and Tolerability

No adverse events, including irritation, erythema, or hypersensitivity reactions, were reported during the study. This indicates that ZISHEL XOMAGE (Zishel Bio Inc., Seoul, Korea) was well-tolerated by patients, with no significant side effects observed. The safety profile of these exosome-based products was excellent, further reinforcing their potential as a viable alternative to conventional therapies for AD.

DISCUSSION

This case series highlights the potential efficacy and safety of ZISHEL XOMAGE (Zishel Bio Inc., Seoul, Korea), for managing facial AD. The observed improvements in clinical severity, skin hydration, barrier function, and pruritus suggest that exosome-based therapies may offer a promising alternative to conventional AD treatments. By addressing multiple facets of AD pathophysiology, including inflammation, barrier dysfunction, and immune dysregulation, these formulations provide a multifaceted approach to managing this complex condition.[19]

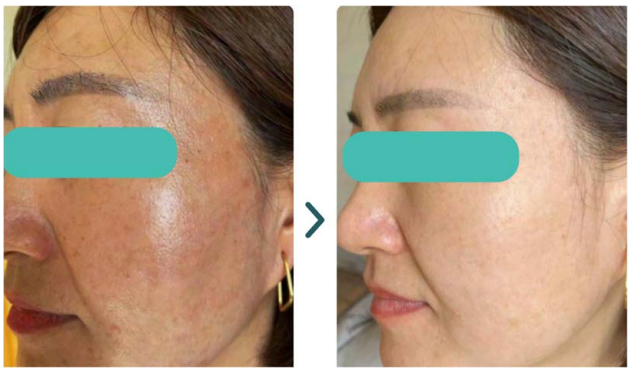

FIGURE 2. Baseline and week 6 photographs of patient B demonstrating substantial resolution of lichenification and significant reduction in facial erythema following treatment with ADMSC-derived exosome (ZISHEL XOMAGE, Zishel Bio Inc., Seoul, Korea).

The mechanisms underlying these improvements align with the known properties of ADMSC-derived exosomes. These nanoscale vesicles carry a diverse cargo of bioactive molecules, including growth factors, cytokines, lipids, and microRNAs, which collectively modulate inflammation, enhance epidermal barrier integrity, and promote tissue repair.[20–22] The significant reduction in TEWL and improved corneometry measurements observed in this study underscore their ability to restore skin barrier function, a critical factor in AD management.

Exosomes offer distinct advantages over conventional therapies. Unlike topical corticosteroids and calcineurin inhibitors, which often target isolated aspects of AD pathophysiology, exosomes address inflammation, barrier dysfunction, and tissue regeneration simultaneously. Their nanoscale size facilitates superior tissue penetration and targeted delivery to keratinocytes and fibroblasts, promoting extracellular matrix remodeling, angiogenesis, and oxidative stress protection.[23] In addition, their noncellular nature minimises risks associated with immune rejection and tumorigenesis, making them a safer and more scalable alternative to cell-based therapies.[24–26]

The cosmetic classification of ZISHEL XOMAGE is particularly advantageous, as it provides patients with an accessible, nonprescription option for managing AD symptoms. This accessibility may improve adherence to treatment regimens and enhance long-term outcomes for patients with chronic AD. The observed 70% reduction in pruritus severity is especially noteworthy, as itch is often the most distressing symptom for AD patients and significantly impacts quality of life. This improvement suggests that exosomes may modulate pathways involved in itch sensation, potentially through interactions between cutaneous nerve fibres, immune cells, and keratinocytes.

However, this study has several methodological limitations that must be acknowledged. The photographic documentation lacked standardised lighting and conditions, which may have affected the visual presentation of clinical improvements. This inconsistency highlights the need for standardised photography protocols in future studies to ensure reliable visual documentation. In addition, the relatively small sample size and absence of a control group limit the generalisability of the findings and preclude definitive conclusions regarding the comparative efficacy of exosome-based products.

The distinction between therapeutic claims and cosmetic benefits is crucial in the regulatory landscape. As a cosmetic product, ZISHEL XOMAGE (Zishel Bio Inc., Seoul, Korea) is intended to improve the appearance and condition of the skin rather than to treat or prevent disease. While the observed improvements in skin barrier function and clinical symptoms are promising, they require verification through more rigorous, controlled studies with extended follow-up periods.

Further research is needed to explore the molecular mechanisms underlying the effects of exosome-based therapies. Proteomic and transcriptomic analyses could provide deeper insights into how exosome-derived molecules interact with skin cells to modulate inflammation and promote repair. In addition, the long-term efficacy, safety, and stability of clinical improvements remain to be established, particularly for a chronic condition like AD.

In conclusion, ZISHEL XOMAGE (Zishel Bio Inc., Seoul, Korea), represents a promising cosmetic approach to managing

facial AD, with observed improvements in skin barrier function and clinical symptoms. However, the limitations of this study, including the small sample size and lack of standardised assessments, necessitate cautious interpretation of the results. Larger, controlled studies with extended treatment periods and standardised outcome measures are essential to confirm these findings and establish the role of exosome-based products in AD management.

REFERENCES

1. Luger T, Amagai M, Dreno B, et al. Atopic dermatitis: role of the skin barrier, environment, microbiome, and therapeutic agents. *J Dermatol Sci* 2021;102:142–157
2. Bylund S, Kobyletzki LB, Svalstedt M, et al. Prevalence and incidence of atopic dermatitis: A systematic review. *Acta Derm Venereol* 2020;100:adv00160
3. Kim BJ, Lee SY, Kim HB, et al. Environmental changes, microbiota, and allergic diseases. *Allergy Asthma Immunol Res* 2014;6:389–400
4. Lugović-Mihić L, Meštrović-Štefekov J, Potočnjak I, et al. Atopic dermatitis: Disease features, therapeutic options, and a multidisciplinary approach. *Life (Basel)* 2023;13
5. Luger T, Paller AS, Irvine AD, et al. Topical therapy of atopic dermatitis with a focus on pimecrolimus. *J Eur Acad Dermatol Venereol* 2021;35:1505–1518
6. Lax SJ, Harvey J, Axon E, et al. Strategies for using topical corticosteroids in children and adults with eczema. *Cochrane Database Syst Rev* 2022;3:Cd013356
7. Coondoo A, Phiske M, Verma S, et al. Side-effects of topical steroids: A long overdue revisit. *Indian Dermatol Online J* 2014;5:416–425
8. Dabrowska S, Andrzejewska A, Janowski M, et al. Immunomodulatory and regenerative effects of mesenchymal stem cells and extracellular vesicles: Therapeutic outlook for inflammatory and degenerative diseases. *Front Immunol* 2020;11:591065
9. Di Bella MA. Overview and update on extracellular vesicles: Considerations on exosomes and their application in modern medicine. *Biology (Basel)* 2022;11
10. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science* 2020;367
11. Moghassemi S, Dadashzadeh A, Sousa MJ, et al. Extracellular vesicles in nanomedicine and regenerative medicine: A review over the last decade. *Bioact Mater* 2024;36:126–156
12. Marote A, Teixeira FG, Mendes-Pinheiro B, et al. Mscsderived exosomes: Cell-secreted nanovesicles with regenerative potential. *Front Pharmacol* 2016;7:231
13. Cao G, Chen B, Zhang X, et al. Human adipose-derived mesenchymal stem cellsderived exosomal microrna-19b promotes the healing of skin wounds through modulation of the ccl1/tgf-β signaling axis. *Clin Cosmet Investig Dermatol* 2020;13: 957–971
14. Jiao YR, Chen KX, Tang X, et al. Exosomes derived from mesenchymal stem cells in diabetes and diabetic complications. *Cell Death Dis* 2024;15:271
15. Simpson E, Bissonnette R, Eichenfield LF, et al. The validated investigator global assessment for atopic dermatitis (viga-ad): The development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis. *J Am Acad Dermatol* 2020;83:839–846
16. Simpson EL, Bissonnette R, Paller AS, et al. The validated investigator global assessment for atopic dermatitis (viga-ad™): A clinical outcome measure for the severity of atopic dermatitis. *Br J Dermatol* 2022;187:531–538
17. Voegeli R, Cherel M, Schoop R, et al. A comprehensive comparison of facial skin hydration based on capacitance and conductance measurements in chinese women. *Int J Cosmet Sci* 2022;44:703–718
18. Fluhr JW, Wiora G, Nikolaeva DG, et al. In vivo transepidermal water loss: Validation of a new multi-sensor open chamber water evaporation system tewameter tm hex. *Skin Res Technol* 2023;29: e13307
19. Kim J, Kim BE, Leung DYM. Pathophysiology of atopic dermatitis: Clinical implications. *Allergy Asthma Proc* 2019;40: 84–92
20. Hade MD, Suire CN, Suo Z. Mesenchymal stem cell-derived exosomes: Applications in regenerative medicine. *Cells* 2021:10
21. Yang B, Lin Y, Huang Y, et al. Extracellular vesicles modulate key signaling pathways in refractory wound healing. *Burns Trauma* 2023;11:tkad039
22. Yadav S, Maity P, Kapat K. The opportunities and challenges of mesenchymal stem cells-derived exosomes in theranostics and regenerative medicine. *Cells* 2024;13
23. Zhang B, Bi Y, Wang K, et al. Stem cell-derived extracellular vesicles: Promising therapeutic opportunities for diabetic wound healing. *Int J Nanomedicine* 2024;19:4357–4375
24. Qin X, He J, Wang X, et al. The functions and clinical application potential of exosomes derived from mesenchymal stem cells on wound repair: A review of recent research advances. *Front Immunol* 2023;14:1256687
25. Miron RJ, Estrin NE, Sculean A, et al. Understanding exosomes: Part 2-emerging leaders in regenerative medicine. *Periodontol 2000* 2024;94:257–414
26. Shin KO, Ha DH, Kim JO, et al. Exosomes from human adipose tissuederived mesenchymal stem cells promote epidermal barrier repair by inducing de novo synthesis of ceramides in atopic dermatitis. *Cells* 2020;9