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Polynucleotides for Facial Erythema and Skin Barrier Repair in Adult Atopic Dermatitis: A Pilot Study

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ABSTRACT

Background: Facial erythema in adult patients with atopic dermatitis (AD) presents a persistent therapeutic challenge, often resistant to conventional treatment. Polynucleotides (PN) have anti-inflammatory and tissue-repair properties and are being explored for inflammatory dermatoses.

Objectives: To evaluate the clinical and biophysical efficacy and safety of intradermal PN injections for facial erythema and barrier dysfunction in adults with AD.

Methods: This prospective pilot study included 19 adults with mild-to-moderate AD and visible facial erythema. Participants received three sessions of intradermal PN injections at 3-week intervals. Clinical assessments were performed at baseline and weeks 3, 6, and 10. Objective parameters included erythema index (EI), melanin index (MI), transepidermal water loss (TEWL), corneometer-measured hydration, and skin elasticity (R2, R5, R7). The Investigator Global Assessment (IGA), patient satisfaction, and standardized facial imaging were evaluated.

Results: Significant improvements were observed in TEWL ($\chi^2 = 31.16$, $p < 0.000001$), hydration ($\chi^2 = 14.56$, $p = 0.002$), and EI ($\chi^2 = 26.05$, $p < 0.001$). Skin elasticity showed favorable trends without statistical significance. IGA scores improved significantly ($\chi^2 = 26.02$, $p < 0.00001$), while patient satisfaction increased ($\chi^2 = 3.44$, $p = 0.179$). No serious adverse events were reported.

Conclusion: Intradermal PN injection is a safe and potentially effective option for facial erythema in AD patients, leading to improved clinical and biophysical outcomes. Larger controlled trials are warranted.

Trial Registration: Korean Clinical Trial Registry (KCT): KCT0011301

1 | Introduction

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease characterized by pruritus, eczematous lesions, and skin barrier dysfunction. Although it frequently begins in infancy, its prevalence in adults is increasing, and many patients experience persistent or late-onset symptoms [1]. Among the various manifestations, facial involvement, especially erythema, is of particular concern because of its visibility, psychosocial impact, and resistance to standard therapy [2].

The pathogenesis of facial erythema in AD is multifactorial and involves epidermal barrier disruption, chronic inflammation, and neurovascular dysregulation [3]. Despite the recent success of systemic biologics such as dupilumab (an IL-4 receptor α antagonist), a subset of patients experience new or persistent facial erythema during or after treatment; the etiology of this paradoxical reaction remains unclear, and optimal management strategies are lacking [4].

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Topical treatments and barrier-enhancing agents remain foundational in AD management but often show limited efficacy in addressing persistent erythema and skin texture issues. Recently, minimally invasive injectables, commonly termed “skin boosters,” have gained popularity as adjunctive therapies for improving skin quality and integrity. Among these, polynucleotides (PN) are long-chain DNA fragments extracted from salmon that have demonstrated promising regenerative, anti-inflammatory, and barrier-restoration properties [5, 6].

PN stimulates fibroblast activity, enhances extracellular matrix production, and modulates inflammatory cytokines [5]. Studies have shown that PN improves hydration, elasticity, and skin texture in aged and sensitive skin types [6]. Furthermore, in a recent large-scale physician survey, over 80% of the dermatologists reported that PN were effective in managing facial erythema in inflammatory dermatoses, including AD [7, 8]. Nevertheless, despite the increasing off-label use, robust clinical data supporting the use of PN in AD treatment, particularly for facial involvement, remain scarce.

This pilot study aimed to evaluate the clinical efficacy and safety of intradermal PN injections (Rejuran) for improving facial erythema, skin hydration, elasticity, and barrier function in adult patients with AD.

2 | Materials and Methods

2.1 | Ethics Statement

This study was approved by the Institutional Review Board (IRB) (IRB approval number: 2406-028-605) and conducted in compliance with the Declaration of Helsinki guidelines. Informed consent was obtained from all participants before enrollment in the study. Written informed consent for publication of identifiable images was obtained from all participants whose images are included in this manuscript.

2.2 | Study Design and Participants

This prospective, single-arm pilot study included 20 enrolled and 19 analyzed adult patients diagnosed with AD presenting with facial erythema. One participant withdrew due to personal reasons and was excluded from analysis.

All participants had clinically stable mild-to-moderate AD (Eczema Area and Severity Index [EASI], 1.0–21.0) that was adequately controlled with their ongoing topical and/or systemic therapies prior to study entry [9]. During the study period, these baseline treatments were maintained without any modification, and no new systemic or topical agents were introduced. This approach was intended to evaluate the add-on effects of intradermal PN treatment under stable disease conditions, while minimizing potential bias arising from changes in AD medications. Participants with seborrheic dermatitis, rosacea, or other facial dermatoses were excluded to eliminate confounding causes of erythema. Patients planning to undergo any facial cosmetic procedures during the study period were also excluded.

2.3 | Intervention

Participants received intradermal injections of 2 mL of a PN-containing product (Rejuran) into each cheek at 3-week intervals for a total of three sessions. After facial cleansing and baseline

evaluation, topical anesthetic cream (EMLA) was applied to both cheeks for 30 min. Injections were performed by a single experienced dermatologist, with 0.1 mL administered per point, at 10 points per cheek, totaling 20 injection points per session. Assessments were conducted at baseline (week 0) and at weeks 3, 6, and 10 after treatment.

2.4 | Objective Skin Measurements

All measurements were performed in a controlled environment (temperature $22^{\circ}\text{C} \pm 1^{\circ}\text{C}$; humidity $45\% \pm 5\%$) after a 30 min acclimatization period. Three consecutive readings were taken at each site (bilateral malar regions), and the mean of the right and left cheek values was used for analysis. Transepidermal water loss (TEWL) was measured using a Tewameter TM 300 (Courage + Khazaka electronic GmbH, Cologne, Germany), which reflects epidermal barrier integrity. Skin hydration was assessed using a Corneometer CM 825 (Courage + Khazaka electronic GmbH, Cologne, Germany), which evaluates stratum corneum water content via electrical capacitance. Erythema and melanin index (EI/MI) were measured using a Mexameter MX 18 (Courage + Khazaka electronic GmbH, Cologne, Germany), which quantifies hemoglobin and melanin content by reflectance at wavelengths of 568 and 660 nm. Skin elasticity was evaluated with a Cutometer MPA 580 (Courage + Khazaka electronic GmbH, Cologne, Germany), which applies negative pressure to assess the viscoelastic properties of the skin.

2.5 | Clinical Evaluation

The Investigator Global Assessment (IGA) was performed using a validated six-point scale (0 = clear to 5 = very severe disease), and the average IGA score was calculated from two independent dermatologists. Subjective satisfaction was rated on a five-point Likert scale from “very dissatisfied” to “very satisfied.” Facial imaging was conducted with the Mark-Vu system.

2.6 | Safety Assessment

At each visit, the participants were monitored for adverse reactions through both clinical examination and self-reported symptoms, including erythema, edema, discomfort, or other local skin reactions.

2.7 | Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows version 26. For continuous variables (TEWL, corneal hydration, EI/MI, and skin elasticity), values from both cheeks were averaged. The Friedman test was used to assess within-subject changes over time, followed by the Wilcoxon signed-rank test for pairwise comparisons against the baseline. Statistical significance was defined as $p < 0.05$. The IGA scores from two independent investigators were averaged for analysis, and inter-rater differences were evaluated using the Wilcoxon test. Patient satisfaction scores (5-point Likert scale) were analyzed using nonparametric tests. Data are presented as mean $\pm$ standard error of the mean (SEM).

3 | Results

A total of 19 participants (4 men and 15 women; mean age 38.2 ± 9.7 years) completed the study. The mean disease duration of AD

was 14.6 ± 8.2 years (range 3–32 years, and the mean baseline EASI score was 9.8 ± 5.1 . Participants remained clinically stable on their existing treatments, which were unchanged during the study period. Detailed demographic and clinical characteristics are summarized in Table 1.

3.1 | Tewameter Evaluation

Mean TEWL significantly decreased after PN treatment ($\chi^2 = 31.16$, $p < 0.000001$), with significant reductions at weeks 3, 6, and 10 compared with baseline (Figure 1).

3.2 | Corneometer Evaluation

Skin hydration increased significantly ($\chi^2 = 14.56$, $p = 0.002$), with significant improvements at weeks 6 and 10 (both $p < 0.01$) (Figure 2).

3.3 | Mexameter Evaluation

EI decreased significantly ($\chi^2 = 26.05$, $p < 0.001$), while MI remained unchanged ($\chi^2 = 5.80$, $p = 0.122$) (Figure 3).

3.4 | Cutometer Evaluation

Skin elasticity parameters assessed using the cutometer—R2 (gross elasticity), R5 (net elasticity), and R7 (biological elasticity)—showed a tendency to increase during the early phase of treatment. However, the changes were not statistically significant throughout the study period. The Friedman test demonstrated no significant differences across visits for any of the three parameters (R2: $\chi^2 = 5.40$, $p = 0.145$; R5: $\chi^2 = 2.40$, $p = 0.494$; R7: $\chi^2 = 4.80$, $p = 0.187$), suggesting that while some improvement in skin elasticity was observed in individual cases, the overall effect did not reach statistical significance.

TABLE 1 | Baseline characteristics of participants ($n = 19$).

Variable	Value or n (%)
Age, years	38.2 ± 9.7 (range 24–56)
Sex (male/female)	4 (21.1%)/15 (78.9%)
Duration of AD, years	14.6 ± 8.2 (range 3–32)
EASI score	9.8 ± 5.1 (range 1.0–21.0)
Current treatments	
Dupilumab	5 (26.3%)
JAK inhibitors (upadacitinib or baricitinib)	3 (15.8%)
Topical corticosteroids	12 (63.2%)
Topical calcineurin inhibitors	15 (78.9%)
Oral antihistamines	18 (94.7%)
Oral probiotics	10 (52.6%)
Oral γ -linolenic acid	7 (36.8%)

Note: Values are presented as mean $\pm$ SD (range) or number (%).

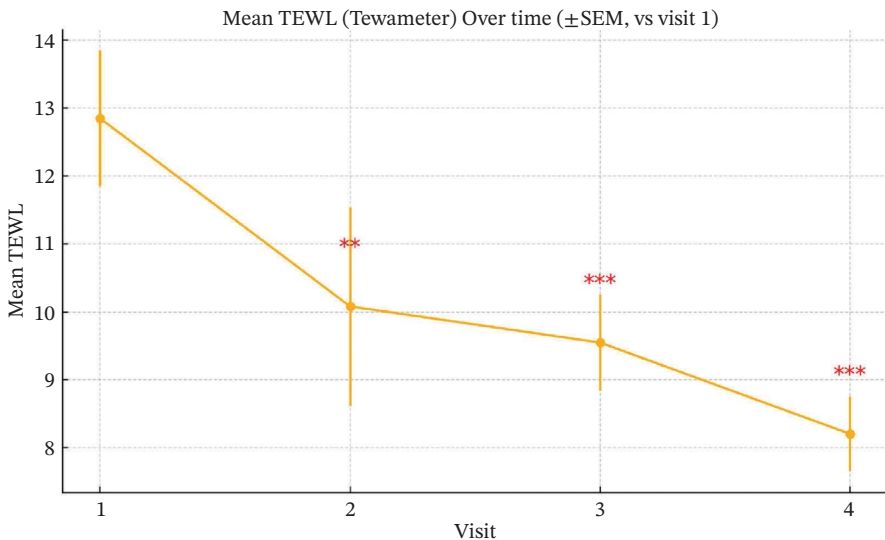


FIGURE 1 | Changes in TEWL over time. Mean TEWL measured by Tewameter decreased significantly after PN treatment. Data are shown as mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. visit 1.

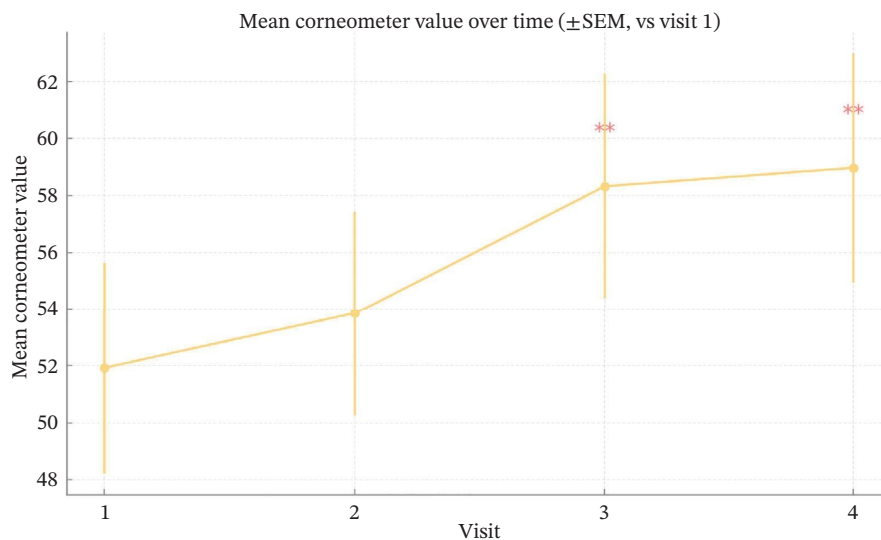


FIGURE 2 | Changes in skin hydration over time. Mean corneometer values increased significantly following PN treatment. Data are shown as mean $\pm$ SEM. ** $p < 0.01$ vs. visit 1.

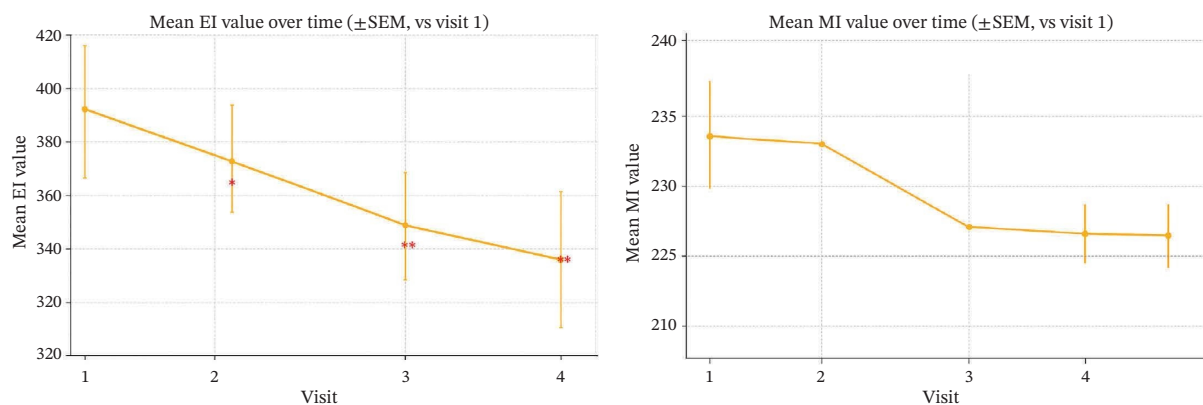


FIGURE 3 | Changes in erythema and melanin index. Erythema index (EI) significantly decreased at all follow-ups, while melanin index (MI) showed no significant change. Data are mean $\pm$ SEM. *** $p < 0.001$ vs. visit 1.

3.5 | IGA Evaluation

The mean IGA score showed a progressive and statistically significant reduction from visit 1 (baseline) to visit 4. The Friedman test revealed a significant difference in IGA scores across visits ($\chi^2 = 26.02$, $p < 0.00001$). Wilcoxon signed-rank post hoc tests demonstrated significant reductions in the IGA scores from baseline at visits 2 ($p < 0.01$), 3 ($p < 0.001$), and 4 ($p < 0.001$) (Figures 4 and 5).

3.6 | Patient Satisfaction Assessment

Patient satisfaction scores gradually increased, though not significantly ($\chi^2 = 3.44$, $p = 0.179$) (Figure 6).

3.7 | Adverse Event Monitoring

No serious adverse events occurred. Transient erythema (26.3%), mild bruising (21.1%), and localized swelling (15.8%) were observed but resolved spontaneously within 3–5 days. In the patient shown in Figure 5(b), acne-like papules on the left chin were pre-existing and outside the injection area; thus, they were not considered treatment-related. No similar eruptions occurred in other participants.

4 | Discussion

AD involving facial lesions imposes a substantial burden on the quality of life of patients, owing to its chronicity, visibility, and emotional impact [1, 2]. Among its manifestations, facial erythema is particularly distressing, as it leads to greater psychosocial impairment than lesions on other body sites [2]. Despite the therapeutic advances represented by biologics such as dupilumab, a notable proportion of patients (20%–30%) continue to suffer from persistent or even paradoxical facial erythema [3, 4]. This highlights the unmet need for alternative or adjunctive treatment modalities that target both inflammation and skin barrier repair.

Our results suggest that intradermal PN injections may represent a promising adjunctive therapy for adult patients with facial AD. Significant improvements were observed in TEWL and stratum corneum hydration, indicating enhanced barrier recovery. The sustained decrease in EI further supports PN's anti-inflammatory and skin-calming potential. Importantly, these effects were achieved without altering baseline AD medications, confirming PN's value as an add-on therapeutic option under stable disease conditions.

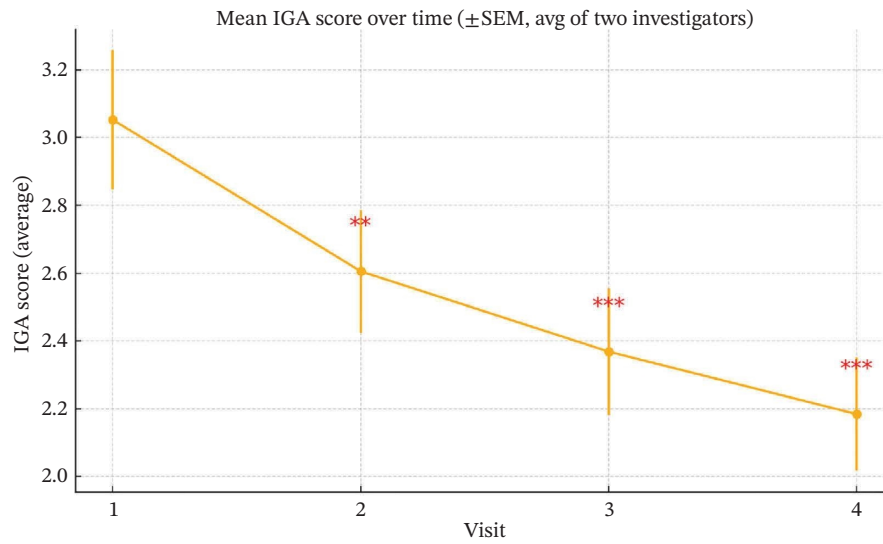


FIGURE 4 | Investigator global assessment scores. Mean Investigator Global Assessment (IGA) scores significantly decreased over time. Values are mean $\pm$ SEM. ** $p < 0.01$, *** $p < 0.001$ vs. visit 1.

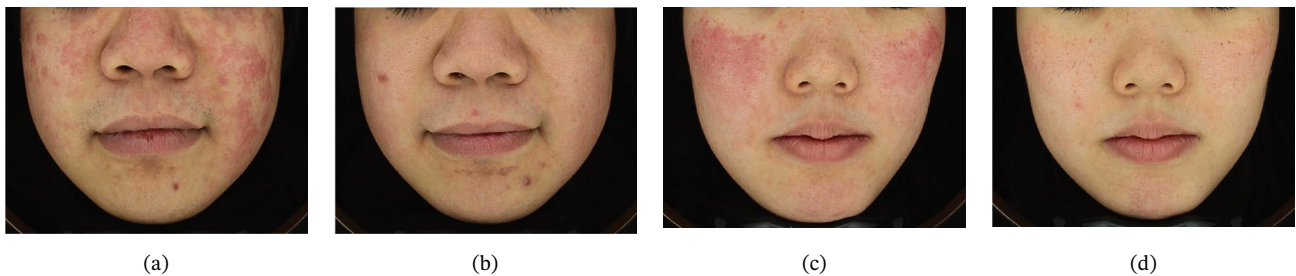


FIGURE 5 | Representative cases of two patients with atopic dermatitis, captured using the Mark-Vu imaging system before and after intradermal PN treatment. (a, c) Baseline images prior to treatment, showing prominent erythema, dryness, and subjective symptoms of pruritus. (b, d) Follow-up images taken 4 weeks after three sessions of intradermal PN injections, demonstrating visible improvements in erythema, desquamation, and overall skin texture, along with reduced pruritus.

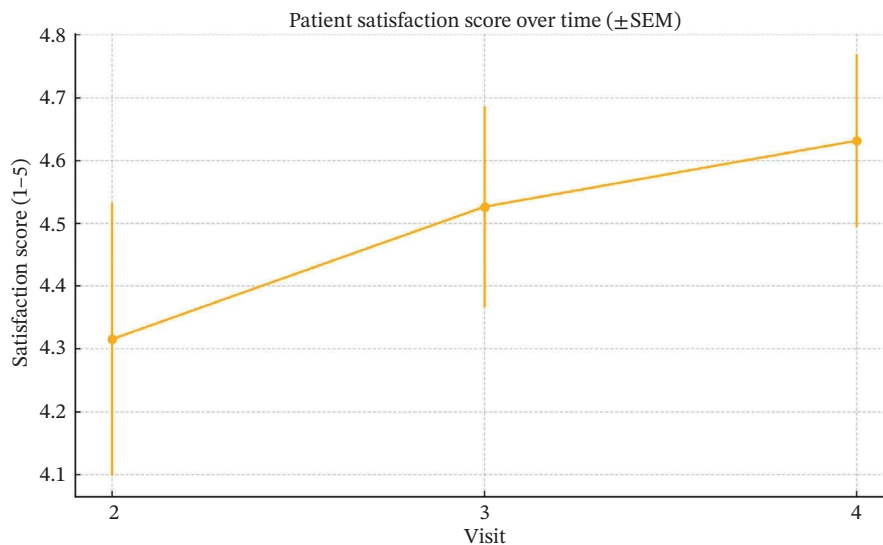


FIGURE 6 | Patient satisfaction scores. Satisfaction scores increased over time but did not reach statistical significance.

PNs are long-chain DNA polymers with regenerative, antioxidant, and anti-inflammatory activities. They activate the adenosine A_2A receptor, which suppresses tumor necrosis factor-

alpha ($TNF-\alpha$) and interleukin-12 (IL-12) while enhancing vascular endothelial growth factor (VEGF)-mediated tissue repair [10]. Additionally, PN modulate NF- κ B, Smad2/3, JNK, and

AKT signaling pathways, promoting cytokine regulation, keratinocyte migration, and dermal remodeling [11–13]. These mechanisms are consistent with the clinical improvements in erythema and barrier function observed in this study, supporting PN's potential role in restoring epidermal homeostasis in AD skin.

FLG plays a central role in maintaining skin barrier integrity by aggregating keratin filaments and contributing natural moisturizing factors through its degradation products [14]. Loss-of-function mutations in the FLG gene are well-established risk factors for early-onset and severe AD. Even in nonmutated cases, FLG expression is often suppressed by inflammatory cytokines such as IL-4, IL-13, and IL-1 β [3, 15]. Restoration of FLG expression after PN treatment indicates the reversal of cytokine-mediated barrier dysfunction and supports the therapeutic potential of PN in reestablishing epidermal differentiation and resilience [16].

Although the elasticity indices (R2, R5, and R7) measured by cut-offs showed an improving trend, statistical significance was not reached, potentially due to the short follow-up duration or interindividual variability. Nevertheless, the IGA scores demonstrated significant clinical improvement, and subjective patient satisfaction increased over time. Importantly, PN injections were well tolerated, with only mild and transient adverse events observed, confirming the safety of this approach, even in compromised AD skin. Given that PNs exert early therapeutic effects by attenuating inflammation and restoring skin barrier function in AD, it is plausible that further improvements in skin elasticity may be achieved when subsequent treatments are administered on this enhanced dermal foundation. Therefore, future studies with extended follow-up periods and larger cohorts are warranted to validate the long-term benefits of PN therapy on skin viscoelasticity in AD patients.

Despite these encouraging findings, several limitations should be acknowledged. This was a pilot study with a small sample size, conducted without a control group or randomization. The short observation period limits the ability to assess long-term outcomes, and quality-of-life parameters were not included. Additionally, all participants were Korean adults, which may restrict generalizability to other populations. Future multicenter, randomized controlled trials with longer follow-up durations are warranted to confirm these preliminary results and to define optimal treatment protocols.

Beyond their therapeutic implications, PNs have garnered attention in aesthetic dermatology as injectable “skin boosters” owing to their ability to enhance skin hydration, elasticity, collagen synthesis, and overall dermal rejuvenation [5, 6]. Clinical studies and expert reviews have reported improvements in skin density, wrinkle depth, and dermal matrix remodeling following PN-based treatments, particularly when combined with hyaluronic acid or delivered in long-chain formulations [16, 17]. A recent systematic review confirmed the efficacy and safety of PN for aesthetic indications, consolidating its role as a regenerative agent in cosmetic dermatology [18]. Our study extends this application to the context of inflammatory dermatoses and highlights its dual utility in improving disease control and cosmetic outcomes.

In patients with facial AD, where the psychosocial burden is high and treatment expectations often include aesthetic improvement, PN may provide a novel, integrated approach that supports both skin health and appearance. Such dual benefits could enhance treatment adherence, patient satisfaction, and the overall quality of life. Additionally, regenerative biologics such as adipose-derived stem cell exosomes are emerging as potential alternatives or complements for managing facial erythema, including dupilumab-associated reactions [4].

To date, no published clinical studies have specifically evaluated the effects of PN in patients with paradoxical facial erythema associated with AD or biologic therapy such as dupilumab. However, recent case-based observations and expert surveys have suggested that PN injections may improve erythema and barrier dysfunction in inflammatory facial dermatoses, including dupilumab-associated reactions, likely due to PN's anti-inflammatory, vascular-stabilizing, and barrier-repair properties. We hypothesize that PN could help normalize vascular reactivity and reduce subclinical inflammation in such cases, providing symptomatic relief and improving barrier recovery. Regarding Malassezia, it is plausible that PN's immunomodulatory effects on the innate immune response and keratinocyte homeostasis could indirectly attenuate Malassezia-associated inflammation; nevertheless, this mechanism has not yet been empirically verified.

In conclusion, this pilot study demonstrated that intradermal PN injections are a safe, well-tolerated, and potentially effective adjunctive therapy for adult patients with AD with facial involvement. PN injections may fulfill an unmet clinical need by addressing both inflammation and barrier dysfunction, offering aesthetic benefits. Further randomized controlled trials with larger cohorts and longer follow-up periods are warranted to validate these findings and define optimal treatment algorithms.

Author Contributions

The author is solely responsible for all aspects of the study, including conceptualization, methodology, data collection and analysis, and manuscript writing.

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Disclosure

The funding body had no role in the study design, data collection, analysis, interpretation, or writing of the manuscript. The author is responsible for the final approval of the manuscript.

Ethics Statement

This study was approved by the Institutional Review Board (IRB) (IRB approval number: 2406-028-605) and conducted in compliance with the Declaration of Helsinki guidelines. Informed consent was obtained from all participants before enrolment in the study.

Conflicts of Interest

Kui Young Park has served as an advisory board member of PharmaResearch Co., Ltd.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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