

Original Article



A Multi-Center, Open-Label, Single-Arm, Prospective Investigator Initiated Trial to Evaluate the Efficacy and Safety of Alitretinoin in Patients With Chronic Hand Eczema in Real-World Practice (DWALG_P401) and Overview of Korean Studies

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ABSTRACT

Background: Chronic hand eczema (CHE) is a debilitating dermatologic condition often refractory to topical corticosteroids (TCS). Although oral alitretinoin has demonstrated efficacy in CHE, real-world multicenter data in Korean populations remain limited.

Objective: To evaluate the real-world efficacy and safety of oral alitretinoin in Korean patients with severe CHE with insufficient response to TCS.

Methods: This multicenter, prospective, open-label study enrolled 146 patients with severe CHE at tertiary hospitals in Korea. Patients received oral alitretinoin (30 mg once daily, with dose reduction to 10 mg permitted) for up to 24 weeks, with observation up to 36 weeks. The primary endpoint was achievement of “clear” or “almost clear” on the Physician’s Global Assessment (PGA) at treatment completion. Secondary endpoints included the modified total lesion symptom score (mTLSS) and Patient’s Global Assessment (PaGA). Safety was evaluated by monitoring adverse events (AEs) and laboratory abnormalities. Efficacy analyses were performed on the full analysis set (n=129).

Results: At treatment completion, 55 patients (42.64%) achieved a PGA response. Improvement increased from week 4 (1.83%) to week 36 (60.87%). PaGA showed consistent improvement, with 17.32% reporting “clear or almost clear” and 28.35% reporting “marked improvement” at treatment completion. mTLSS scores improved by 62.3% at treatment completion and by 75.7% at week 36. In the safety analysis (n=134), 44.03% experienced AEs, most commonly headache (29.10%).

Conclusion: Oral alitretinoin at daily doses of 10 mg or 30 mg demonstrated effective symptom improvement and an acceptable safety profile in Korean patients with CHE in a real-world setting.

Keywords: Alitretinoin; Eczema; Hand dermatoses; Korea

INTRODUCTION

Chronic hand eczema (CHE) is a persistent inflammatory skin disease of the hands, most commonly presenting with erythema, scaling, fissuring, pruritus, and pain¹⁻³. The disease typically follows a relapsing course and can substantially impair daily functioning and quality of life⁴. In addition to its clinical burden, CHE is associated with considerable socioeconomic impact, including reduced work productivity and increased healthcare utilization^{5,6}. While topical corticosteroids (TCS) are commonly used as first-line therapy, a considerable proportion of patients with severe CHE do not achieve satisfactory disease control, prompting consideration of systemic treatment options¹. Moreover, prolonged corticosteroid use is associated with adverse effects, including skin atrophy, and systemic therapy is therefore often required in patients with refractory disease⁷.

Alitretinoin is a pan-retinoid receptor agonist (retinoic acid receptor and retinoid X receptor) approved for the treatment of severe CHE unresponsive to TCS^{8,9}. Its efficacy and safety have been established in randomized controlled trials such as the BACH study¹⁰, which demonstrated a significantly higher response rate with alitretinoin versus placebo. Observational studies such as the TOCCATA study^{11,12} further supported its use in routine practice, particularly in patients with hyperkeratotic disease subtypes^{11,13}.

Despite global evidence, real-world data for alitretinoin in Korean patients are limited¹⁴. Korean CHE populations may exhibit distinctive features compared with Western cohorts, owing to differences in genetic background, occupational exposures, and real-world access to systemic retinoids, along with a higher prevalence of hyperkeratotic disease^{13,15}. To date, only six small, mostly single-center Korean reports have been published, and most did not formally compare outcomes with and without concomitant TCS (**Table 1**)^{13,14,16-19}.

Accordingly, this study aimed to evaluate the effectiveness and safety of oral alitretinoin (10 mg or 30 mg) in Korean patients with

severe CHE in real-world clinical settings, including its therapeutic effect as monotherapy without concomitant TCS. The findings are expected to provide evidence supporting optimal management of CHE in Korean dermatological practice.

MATERIALS AND METHODS

Study design and participants

This is an open-label, prospective, multicenter, single-arm, investigator-initiated study conducted in Korea. The study was conducted from April 2022 to February 2024, during which 160 patients were screened across 12 institutions, and 146 who met the eligibility criteria were enrolled.

Study participants included adult patients aged between 19 and 75 years who were diagnosed with severe CHE. Eligible patients had experienced CHE persisting ≥ 12 weeks or relapsing ≥ 2 times within 48 weeks. All participants had previously undergone at least four weeks of treatment with high-potency TCS without satisfactory response. The diagnosis and severity of CHE were assessed by dermatologists using the Physician's Global Assessment (PGA). PGA (clear/almost clear/mild/moderate/severe) was defined by combining: 1) clinical features (erythema, scaling, lichenification/hyperkeratosis, vesication/edema/fissures, pruritus/pain), 2) intensity (absent/mild/moderate/severe), and 3) area involved. Detailed criteria are listed in **Supplementary Table 1**. Only patients rated as “severe” were included.

Patients were excluded if they had bacterial, fungal, or viral infections of the hands, unavoidable allergic contact dermatitis, or other dermatologic conditions that could interfere with study evaluation. Additional exclusion criteria included the presence of psoriasis or atopic dermatitis requiring treatment, active liver or renal disease, uncontrolled dyslipidemia, vitamin A toxicity, or a history of psychiatric disorders such as depression. Individuals with pancreatitis or signs suggestive of pancreatitis, hematologic abnormalities, or hypersensitivity to retinoids or

Table 1. Summary of previous studies on the use of alitretinoin to treat hand eczema in Korea

Study	Study design	Number (analyzed)	Dose/regimen	Primary endpoint	Efficacy	Relapse	Safety highlights	Product
Kwon et al. ¹⁹ (2016)	Prospective, single-center	27	10 mg or 30 mg QD × 12 wk	PGA (clear/almost clear) responders at 12 wk	44.40%	25%	AEs 51.9% (headache 40.7%); no significant lab abnormalities	Alitoc®
Kim et al. ¹⁴ (2019)	Retrospective, single-center	65	30 mg QD × 24 wk	PGA (clear/almost clear) responders at 24 wk	61.50%	NR	Headache 16.9%; no serious AEs	NR
Jo et al. ¹⁷ (2019)	Retrospective, single-center	46	10 mg or 30 mg >8 wk (mean 180 days)	PGA (clear/almost clear) responders at ≥8 wk	82.60%	NR	AEs 28.3% (headache 13.0%, GI 8.7%, xerosis 6.5%); hypertriglyceridemia 28.3%	NR
Cheon et al. ¹⁸ (2019)	Retrospective, single-center	107	10 mg or 30 mg QD × 12 wk	PGA (clear/almost clear) responders at 12 wk	84.21% vs. 46.00% (with/without TCS)	41.7% vs. 52.2% (with/without TCS)	AEs 43.9% (headache 34.8%, xerosis 10.3%); no serious AEs	Alitoc®
Lee et al. ¹³ (2019)	Retrospective, single-center	46	10 mg or 30 mg QD or QOD (mean 14 wk)	PGA (clear/almost clear) responders at ≥4 wk	61.10%	63.60%	AEs 47.3% (headache 10.9%, flushing 9.1%, xerosis 9.1%); no serious AEs; mild elevation of liver enzymes 7.3%; LDL 7.3%; hypertriglyceridemia 5.5%	NR
Seol et al. ¹⁶ (2021)	Retrospective, two centers	137	10 mg or 30 mg	PGA improvement at 12 wk	59.90%	17.85%	AEs 39.4% (headache, GI, flushing, xerosis); no significant lab abnormalities; no serious AEs	NR

QD: once every day, PGA: Physician's Global Assessment, AE: adverse event, NR: not reported, GI: gastrointestinal, TCS: topical corticosteroids, QOD: once every other day, LDL: low-density lipoprotein.

study drug components were also excluded.

Patients who had received ultraviolet B therapy, psoralen plus ultraviolet A, systemic corticosteroids, systemic retinoids, or immunosuppressants within four weeks prior to baseline were excluded. Likewise, the use of systemic azoles, erythromycin, clarithromycin, tetracyclines, or herbal remedies such as St. John's Wort within 2 weeks prior to baseline was prohibited. Patients requiring any prohibited concomitant medications during the study were also excluded, as were pregnant or breastfeeding women, and individuals with known allergies to soy, peanuts, or any ingredients in the investigational product.

Women and men of reproductive potential were enrolled only if they were fully informed of the teratogenic risks associated with retinoid use and agreed to use dual contraception methods throughout the study period, starting at least 4 weeks before the first dose and continuing for at least 4 weeks after the last dose. Pregnancy testing and contraceptive counseling were mandatory prior to treatment initiation.

All enrolled patients received oral alitretinoin (Aliga Soft cap; Daewoong Pharmaceutical Co., Ltd., Seoul, Korea) at a dose of 30 mg once daily after meals. Dose reduction to 10 mg per day was permitted for patients who experienced adverse events (AEs) considered manageable with symptomatic therapy. Supportive treatments, including oral antihistamines or acetaminophen, were permitted for temporary symptom relief. The use of emollients and TCS was allowed at the investigator's discretion; in contrast, systemic corticosteroids, systemic retinoids, immunosuppressive agents, and phototherapy were not permitted at any time during the study.

Treatment

Eligible patients received oral alitretinoin (Aliga Soft cap 30 mg or 10 mg; Daewoong Pharmaceutical Co., Ltd.) until achievement of the predefined treatment goal, defined as "clear" or "almost clear" on the PGA, with a maximum treatment duration of 24 weeks. Treatment was discontinued earlier if the PGA remained classified as "severe" at week 12 or if the treatment goal was not achieved by week 24. Re-treatment was permitted in cases of relapse at the investigator's discretion, and patients were followed for up to 36 weeks. Dose adjustments between 10 mg and 30 mg were allowed according to individual tolerability. The use of emollients and TCS was permitted, whereas systemic corticosteroids, systemic retinoids, immunosuppressive agents, and phototherapy were not allowed during the study period.

Efficacy and safety assessments

Efficacy analyses were conducted using an observed-case approach. At each visit, proportions were calculated with the number of patients who had a non-missing assessment at that visit as the denominator. The primary efficacy endpoint was the proportion of patients who achieved the predefined treatment goal of "clear" or "almost clear" according to the PGA at the end of treatment. Secondary efficacy endpoints included changes in the modified total lesion symptom score (mTLSS), Patient's Global Assessment (PaGA), and the relapse rate among patients who achieved the treatment goal. The PGA was assessed on a 5-point scale (clear, almost clear, mild, moderate, and severe), while the PaGA was evaluated using a 6-point patient-reported outcome scale (clear, almost clear, marked improvement, moderate

improvement, no change, and worsening). The mTLSS was calculated by summing scores for 5 clinical features (erythema, scaling, lichenification/hyperkeratosis, edema, and fissuring), each graded from 0 to 3 per hand.

Safety outcomes included treatment-emergent adverse events (TEAEs), adverse drug reactions (ADRs), serious adverse events (SAEs), and serious adverse drug reactions (SADRs). TEAEs were defined as any new or worsening events occurring after the first dose of study medication, regardless of causality. ADRs were recorded when a causal relationship to the study drug was assessed as certain, probable, possible, conditional/unclassified, or unassessable/unclassifiable. The assessment of causality was performed by the investigator. Blood samples were collected to assess liver function, lipid profiles, and hematologic parameters.

Statistical analysis

The full analysis set (FAS) comprised all patients who received at least one dose of alitretinoin and had at least one post-baseline efficacy assessment. The per-protocol set (PPS) included patients who completed the study without major protocol deviations. Safety analyses were performed in all patients who received at least one dose of the study drug (Safety Set). Descriptive statistics were used to summarize demographic and baseline characteristics. Categorical variables are presented as frequencies and percentages, whereas continuous variables are expressed as mean $\pm$ standard deviation or median (range), as appropriate. Efficacy analyses were conducted using observed-case data. For the primary endpoint, the proportion of patients achieving the treatment goal was estimated and presented with corresponding 95% confidence intervals. The mTLSS changes from baseline were analyzed using paired t-tests. Subgroup analyses by concomitant TCS use were prespecified as exploratory.

All statistical analyses were performed using SAS[®] version 9.4 (SAS Institute Inc., Cary, NC, USA). A *p*-value of less than 0.05 was considered statistically significant.

Ethical approval

This study was approved by the Institutional Review Board (IRB) of each participating center. The representative approval was obtained from the IRB of the corresponding author's institution (Soonchunhyang University Bucheon Hospital; IRB No. 2021-08-005). All participants provided written informed consent prior to enrollment, and the study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Patients

A total of 160 patients were screened, of whom 146 received at least one dose of alitretinoin. Among them, 129 patients comprised the FAS, 134 were included in the safety set, and 55 in the PPS. The study population had a mean age of 46.4 ± 15.42 years, and 54.79% were female. All 146 enrolled patients fulfilled the 'severe' PGA definition as specified in **Supplementary Table 1**. The most common clinical type of CHE was hyperkeratotic (78.77%), followed by vesicular (11.64%) and fingertip (6.85%). Patient demographics and characteristics are shown in **Table 2**.

Efficacy and safety assessment

At the end of treatment, 42.64% of patients in the FAS (55/129) achieved the treatment goal, defined as "clear" or "almost clear" on the PGA. PGA responses improved progressively over time: 1.83% at week 4, 11.11% at week 8, 16.67% at week 12, 59.09% at week 24, and 60.87% at week 36 (**Fig. 1**). The proportion of

Table 2. Baseline patient demographics and characteristics

Characteristics	Values (n=146)
Age (yr)	46.40 $\pm$ 15.42
Sex	
Male	66 (45.21)
Female	80 (54.79)
Duration of disease (yr)	3.68 $\pm$ 5.80
Physician's Global Assessment	
Severe	146 (100.00)
Type of chronic hand eczema	
Hyperkeratotic	115 (78.77)
Vesicular	17 (11.64)
Fingertip	10 (6.85)
Other	4 (2.74)

Values are presented as number (%) or mean $\pm$ standard deviation.

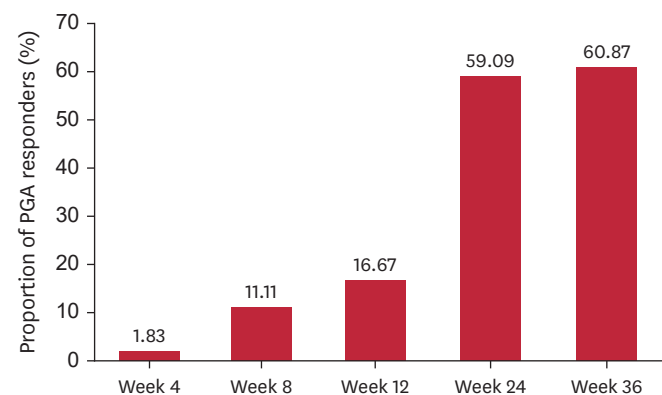


Fig. 1. Clinical improvement with oral alitretinoin in Korean patients with severe chronic hand eczema. Proportion of PGA responders (patients achieving "clear" or "almost clear" status) increased in a time-dependent manner, from week 4 to week 36. PGA: Physician's Global Assessment.

responders was similar between patients who used concomitant TCS (42.34%) and those who did not (44.44%).

Patient-reported outcomes showed a parallel pattern throughout the treatment period. The proportion of patients who rated their disease as “clear or almost clear” on the PaGA was 2.80% at week 4, 11.25% at week 8, 10.61% at week 12, 25.00% at week 24, and 34.78% by week 36 (**Fig. 2**). At the end of treatment visit (n=127), 17.32% of patients reported being “clear or almost clear” and an additional 28.35% reported “marked improvement,” whereas negative assessments such as “no change” and “worsening” consistently decreased over time, with only 1 or 2 patients reporting at later time points.

Lesional severity assessed by mTLSS improved consistently during treatment (**Fig. 3**). The mean mTLSS was reduced by $62.3\% \pm 28.89\%$ from baseline to the end of treatment, and the mean reduction further deepened to 75.7% at week 36, indicating sustained lesion control. Similar degrees of improvement were observed irrespective of concomitant TCS use (-61.6% in users vs. -66.8% in non-users).

Among responders with available follow-up data, no relapse to PGA ‘severe’ was observed through week 36.

Among the 134 patients in the safety set, 59 patients (44.03%) experienced at least one TEAE. Most TEAEs were mild (37.31%) or moderate (11.94%) in intensity. Two SAEs occurred (appendicitis, interstitial lung disease); neither was assessed as related to alitretinoin. Only appendicitis was graded as severe.

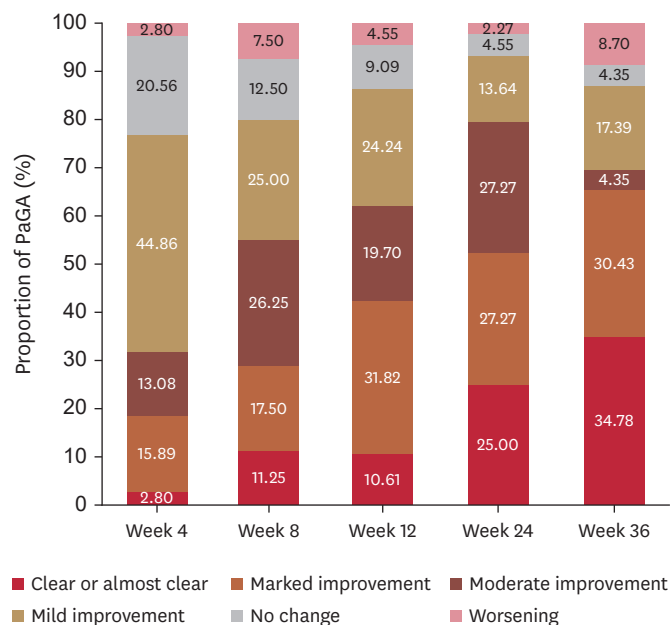


Fig. 2. Time course of PaGA scores. The proportion of patients reporting “clear or almost clear” PaGA increased progressively over time, from week 4 to week 36.
PaGA: Patient’s Global Assessment.

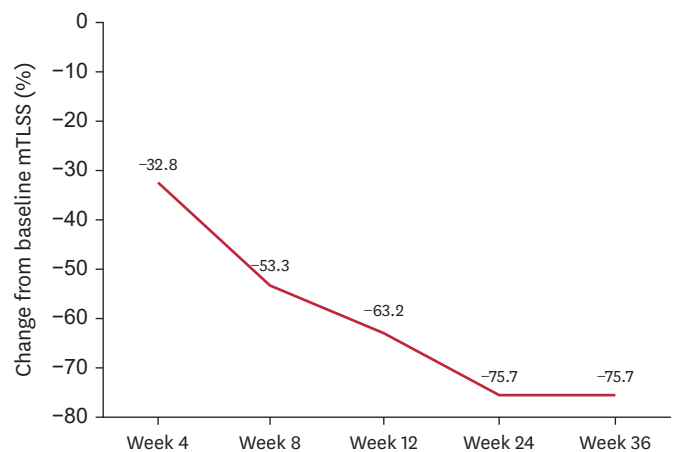


Fig. 3. Time course of lesional improvement based on mTLSS. Mean percent change from baseline mTLSS decreased progressively from week 4 to week 36. mTLSS: modified total lesion symptom score.

Table 3. Reported adverse drug reactions

Adverse reaction*	Values (n=134)
Headache	39 (29.10)
Flushing/hot flush	7 (5.22)
Nausea	3 (2.24)
Xeroderma	2 (1.49)
Others†	7 (5.22)

Values are presented as number (%).

*Multiple nominations possible.

†One case each of blurred vision, cystitis, dry mouth, eczema, erythema, hand dermatitis, and pruritus.

No life-threatening events or deaths were reported, and no SADRs occurred. ADRs were reported in 51 patients (38.06%), most commonly headache (29.1%), followed by flushing, nausea, and xeroderma (**Table 3**). Laboratory monitoring revealed small, clinically manageable increases in total cholesterol and triglycerides and minor liver enzyme changes.

DISCUSSION

CHE is a debilitating, relapsing inflammatory disorder that often persists despite appropriate topical therapy and allergen/irritant avoidance^{12,20}. It imposes a substantial psychosocial and economic burden on affected individuals^{21,22}. Approximately 5%–7% of patients progress to severe disease, and 2%–4% remain refractory despite adequately administered topical treatment. For these patients, systemic therapies that are effective and reasonably safe over a long-term course are needed. Oral alitretinoin is currently the only systemic agent with consistent evidence from randomized trials and large observational cohorts²³. However, most available data pertain to the originator formulation, and current treatment guidelines are likewise grounded in this evidence. In contrast, prospective clinical studies, including randomized trials specific

to generic formulations have not been published, underscoring the need for country-specific, real-world evidence.

This prospective, multicenter study across 12 Korean dermatology centers showed that once-daily oral alitretinoin using a Korean generic formulation resulted in clinically meaningful improvement in patients with severe CHE refractory to potent TCS.

In the FAS, 42.64% achieved a PGA of “clear” or “almost clear” at the end of treatment, with continued accrual of response to week 36. Patient-reported PaGA and mTLSS showed a parallel pattern, underscoring the importance of treatment duration and adherence in CHE¹⁶. This time-dependent accrual of response was broadly consistent with the pivotal BACH trial and the large TOCCATA cohort^{10,12,16,24,25}, despite cessation of active therapy at week 24 for nonresponders and observation thereafter. These data suggest that the clinical efficacy of alitretinoin can be maintained under routine clinical practice conditions in Korea.

The safety profile of the generic preparation was in line with known retinoid class effects for alitretinoin: headache was the most frequently reported event, TEAEs were mostly mild to moderate, and laboratory changes in lipids and liver enzymes were modest and manageable. The proportion of patients with headache was higher in this study than in some earlier reports ranging from 7.5% to 27%^{10,22,25,26}. No new or unexpected safety signals were identified, and the overall pattern fell within ranges reported in originator-based studies^{13,14,16,49}. These findings support the feasibility of alitretinoin therapy in Korean patients with CHE.

Concomitant TCS use did not materially change clinical outcomes in this study. This contrasts with a prior Korean 12-week retrospective series in which standardized high-potency TCS appeared to yield an approximately two-fold higher response rate compared with alitretinoin monotherapy²⁷. The difference is likely driven by treatment duration; the previous study evaluated a 12-week course, whereas our protocol allowed up to 24 weeks of alitretinoin therapy. Notably, systemic alitretinoin administered for an extended period of approximately 6 months may serve as an effective therapeutic option capable of inducing remission and delaying relapse, even in the absence of concomitant TCS.

As summarized in **Table 1**, 6 Korean reports have evaluated oral alitretinoin in practice. Except for one prospective single-center trial¹⁹, most were retrospective and single-center studies, with relatively small sample sizes. Reported response rates varied (approximately 44%–84%), often comparable to or numerically higher. Heterogeneity likely reflects: 1) selection and information bias in retrospective designs (e.g., preferential capture of good responders and less stringent, non-blinded outcome ascertainment); 2) inclusion of mixed baseline severities versus our “severe-only” cohort; 3) mandated, high-potency TCS co-treatment in some studies that may inflate short-term clearance¹⁸; and

4) differences in morphologic subtype distribution—particularly hyperkeratotic subtype known to be recalcitrant¹³—may shift response estimates.

Cheon et al.¹⁸ reported high relapse rates at 12 weeks regardless of concomitant TCS use. In contrast, none of our responders among patients with available follow-up data relapsed to PGA “severe” during 36-week observation following a 24-week treatment plan. These findings suggest that longer treatment duration is needed; a 12-week course may be insufficient to maintain remission in chronic, occupationally driven CHE, whereas sustained, adequately long treatment appears to better stabilize disease control²⁷.

Product attribution was seldom specified in prior Korean reports; two studies explicitly evaluated the originator formulation (Alitoc; GlaxoSmithKline, Seoul, Korea)^{18,19}, whereas four did not report the product (**Table 1**). Although multiple generics entered the Korean market after 2020 on the basis of bioequivalence in healthy volunteers, multicenter, prospective data in actual Korean CHE patients have remained sparse. This study is the first large, multicenter, prospective real-world study conducted after generic launch, and it showed that a locally available generic can achieve efficacy and tolerability numerically similar to those reported for the originator in Korean practice settings.

Prior Korean reports rarely stratified outcomes by concomitant TCS, and one comparative analysis suggested approximately a two-fold higher response with standardized high-potency TCS co-therapy versus alitretinoin alone¹⁸. By contrast, this multicenter prospective cohort showed comparable improvement in PGA and mTLSS irrespective of TCS use. These findings indicate that oral alitretinoin treatment for an extended period of 6 months provides clinically meaningful benefits as monotherapy under routine practice and supports its steroid-sparing role in severe CHE.

This study has several limitations. First, it was an open-label, single-arm study without a comparator, so placebo effects and regression to the mean cannot be excluded. Second, recruitment was conducted only at tertiary dermatology centers, so selection bias toward patients with more severe or treatment-refractory disease is possible. Third, although the study was designed to reflect routine clinical practice, the sample size and 36-week follow-up may still have been insufficient to detect late relapses or rare AEs. Fourth, patient-reported outcomes such as PaGA were collected in an unblinded setting and may have been influenced by expectation. Fifth, because all participants were Korean, generalizability to other ethnicities and healthcare systems may be limited. Finally, as concomitant TCS use was investigator-directed in an open-label setting, exposure to TCS was neither randomized nor protocol-standardized. Therefore, subgroup results by TCS are exploratory and descriptive. In addition, functional

outcomes and biomarkers predictive of treatment response were not evaluated. Despite these limitations, the real-world, multicenter design provides practice-level evidence that complements randomized trials and supports oral alitretinoin as a practical option for Korean patients with CHE who do not respond adequately to potent TCS^{12,15}.

To our knowledge, this is the first prospective, multicenter, real-world study evaluating a locally available generic formulation of oral alitretinoin, rather than the original branded product in Korea. The generic demonstrated efficacy and a safety within the ranges previously reported for originator-based studies. Moreover, clinical improvement was similar with or without concomitant TCS, indicating that alitretinoin provides meaningful benefit as monotherapy and can serve as a steroid-sparing option in routine practice. These findings support the use of generic alitretinoin as a pragmatic treatment for severe CHE in Korea.

Further large-scale randomized controlled trials and longer-term observational studies with head-to-head comparisons with the originator product, longer follow-up to define relapse and retreatment strategies, and incorporation of patient-reported outcomes to capture the full benefit of treatment are needed.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

PGA definition

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