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ORIGINAL RESEARCH

A Prospective Observational Study to Evaluate the Actual Use of 1% Pimecrolimus in Chinese Patients with Mild-to-Moderate Atopic Dermatitis Affecting Sensitive Skin Areas

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Introduction: Atopic dermatitis (AD) is a common inflammatory skin disorder that affects both children and adults, characterized by pruritus and scaly, dry eczematous lesions. This study aimed to gather knowledge on the actual use and effectiveness of Pimecrolimus (PIM) in Chinese patients with mild-to-moderate AD affecting sensitive skin areas in routine clinical practice.

Methods: This multicentre and non-interventional study included 130 subjects from China, divided into two age groups (2–12 years and ≥12 years). The primary endpoint was the change in SCORAD index, in AD areas from inclusion to the end of the PIM treatment period.

Results: The primary efficacy analysis showed a significant reduction in the SCORAD index from baseline to the end of the PIM treatment period ($p < 0.0001$). The mean change in SCORAD index (SD) from baseline at visit 2 and visit 3 was −15.4 (10.50) and −18.6 (11.57), respectively. The mean Investigator's Global Assessment (IGA) score decreased from 2.3 at baseline to 0.7 at the end of the study, while the mean itching score decreased from 4.7 at baseline to 0.9 at the end of the study. The mean duration of PIM use was 38.3 days, with similar durations for patients above and below 12 years. There was progressive improvement in the quality of life of the patients with PIM treatment. The median time to first flare was 100 days and no adverse drug reactions or significant adverse events were reported during the study.

Discussion: This study provides robust real-world evidence that PIM 1% cream is effective for the treatment of mild-to-moderate AD in Chinese patients, particularly in sensitive skin areas and paediatric population. PIM also offers a TCS-sparing approach, making it a valuable option for managing mild-to-moderate AD.

Keywords: atopic dermatitis, pimecrolimus, China, SCORAD index, non-interventional study

Introduction

Atopic dermatitis (AD) is one of the most common inflammatory skin disorders affecting approximately 12% of children and 7.2% of adults.[1] It is a chronic, relapsing inflammatory skin disease characterized by pruritus and scaly, dry eczematous lesion.[2] Along with its financial burden, AD imposes a significant social, academic, and occupational

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burden, severely impacting the patient's quality of life.[3] If left untreated, AD leads to atopic march resulting in asthma and allergic rhinitis.[4] The prevalence of AD in the Asia-Pacific region is around 10.1% with nearly 88% of the paediatric patients experiencing either mild or moderate AD.[5] As compared to mild AD, subjects with moderate AD report a higher disease burden, specifically in terms of itch, pain, sleep disturbance, anxiety, depression, and health-related quality of life.[6] A 2014 survey in China reported the prevalence of AD to be 12.94% in children aged 1–7 years and 30.48% in infants aged 1–12 months.[7]

Long-term management of AD involves reducing the skin inflammation and repairing the defective skin barrier. Topical moisturizers, topical anti-inflammatory medications (eg, corticosteroids, calcineurin inhibitors), allergen/irritant avoidance, and treatment of skin infections form the mainstay for treatment of paediatric patients.[8] Topical corticosteroids (TCS) are effective for the treatment of AD but come with several limitations. Long-term usage of TCS is associated with side effects like tachyphylaxis, corticosteroid addiction, increased risk of infections and skin atrophy.[9] Moreover, Corticophobia amongst the parents and caregivers of the patients also leads to reduced compliance during treatment with TCS.[10] Furthermore, their use in thin and sensitive skin areas (eg, face, neck, intertriginous sites, anogenital area) is not recommended since these areas have greater absorption capacities compared to other areas.[11] Topical calcineurin inhibitors (TCI) offer a safer alternative to TCS, providing similar efficacy to low-to-mid potency TCS, without the same limitations.[2]

Pimecrolimus 1% (PIM) is a TCI, which selectively inhibits the production and release of pre- inflammatory cytokines and mediators by pre-T cells and macrophages. PIM binds to the intracellular protein macrophilin-12 (FK506-binding protein) and inhibits the activity of calcineurin, a phosphatase enzyme involved in T-cell activation. Inhibition of calcineurin prevents the subsequent dephosphorylation and nuclear translocation of nuclear factor of activated T cells (NF-AT), thereby interfering with the transcription of various pro-inflammatory cytokine genes resulting in reduced inflammation and immune response in AD.[12,13]

The safety and efficacy of PIM has been established by many studies in children and adults, including the 5-year PETITE study in infants.[14] A sub-group analysis of the PETITE study focusing on Chinese patients showed an early and sustained efficacy of PIM in this sub-population with a substantial corticosteroid-sparing effect in patients with AD.[15] PIM has been approved in China since 2005 and recently became the only TCI approved for the treatment of AD in infants ≥ 3 months of age. A consensus among experts in China recommends the use of PIM for patients with mild-to-moderate AD. The treatment algorithm proposed aims to address concerns about corticophobia—the fear of side effects from TCS—and suggests applying PIM twice daily to affected areas until symptoms resolve.[2]

Little evidence is available in literature on the use of PIM in Chinese population. Non-interventional studies are considered as an expedient tool to reflect the use under real conditions. This non-interventional study (NIS) was designed with the primary objective to gather knowledge on the actual use and effectiveness of PIM in Chinese patients with mild-to-moderate AD affecting sensitive skin areas in routine clinical practice.

Methods

Study Design

This was a multicentre, prospective, non-interventional study done in patients of Chinese ethnicity. After the clinical decision was made to prescribe PIM to a patient according to the Package Insert, the Investigator considered recruiting the patient into the NIS. The decision was made to prescribe PIM previously and independent of the decision to include the patient in the NIS. Enrolled patients were divided into two groups: (i) 2–12 years and (ii) ≥12 years. Signed informed consent from the patient or parent(s) or legal guardian(s), in compliance with local requirements, was obtained before the study. Three study visits were planned: (i) inclusion (day 0, Visit 1); (ii) investigators assessment of treatment failure or success (end of treatment-EOT, visit 2) and (iii) end of study (EOS, visit 3). In the treatment period with PIM, no other therapy was allowed. The maintenance period was at least 3 months and, if needed, patients could be treated according to the clinical practice and physician's judgment. The total duration of the study (treatment + maintenance) was around 6 months (Figure 1).

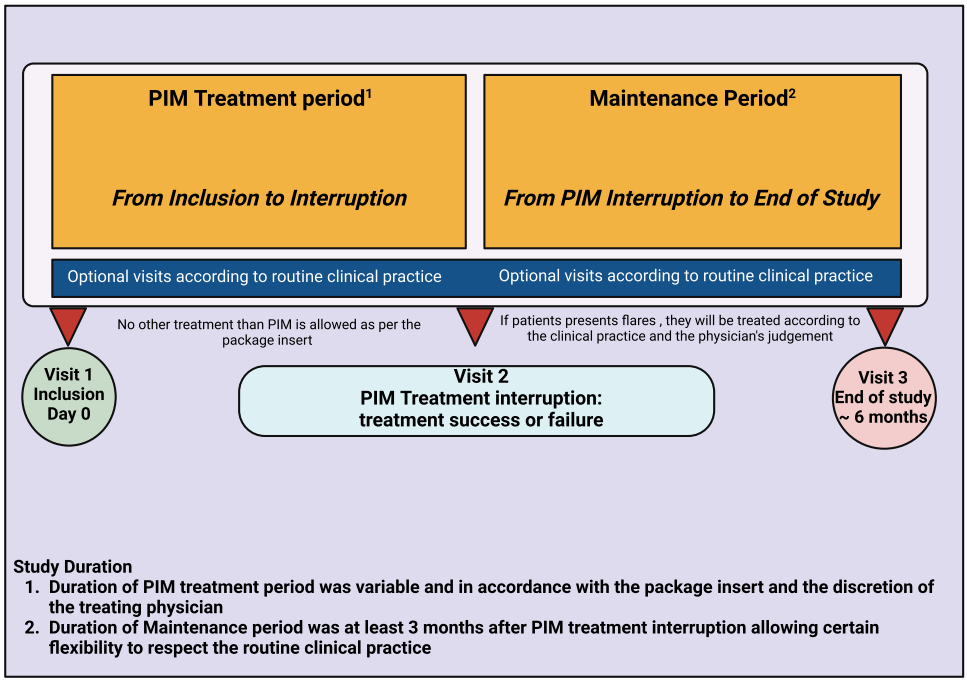

Figure 1 Schematic of Study Design.

Patients

The main inclusion criteria were: (i) patients that have been prescribed PIM according to the package insert and independently from patient's enrolment into the study, (ii) age ≥2 years, (iii) SCORAD index <50 for patients between 2 and 12 years; patients aged ≥13 must have AD affecting sensitive skin areas (eg, face, neck, intertriginous sites, anogenital area), SCORAD index <50 and IGA ≤ 3 in sensitive skin areas. The main exclusion criteria were: (i) patients for whom PIM was not recommended according to the package insert (patients allergic to PIM or any of its components), (ii) patients with severe AD (SCORAD index ≥ 50 or IGA in sensitive skin > 3), (iii) patients who were receiving systemic glucocorticosteroids, antibiotics, antifungals, immunomodulators, antihistamines, and ultraviolet radiation therapy within the last 4 weeks before inclusion, (iv) patients who were receiving any topical AD-effective drugs within the last 2 weeks before inclusion, (v) pregnant and/or breast-feeding women, (vi) patient or parent/ legal guardian (as applicable) that were not able to fulfil study requirements according to investigators' opinion and (vii) patient or parent/ legal guardian (as applicable) who refused to participate in the study.

Endpoints

The primary endpoint of this study was the change in SCORAD index in the AD areas from inclusion to end of PIM treatment period. The secondary endpoints included (i) reduction of AD in defined sensitive skin areas assessed by Investigator's Global Assessment (IGA) from study entry at each subsequent visit until the End of Study Visit, (ii) itching symptoms in sensitive skin areas, (iii) treatment duration, (iv) number of visits during PIM treatment period and during the maintenance phase, (v) Use of treatments for AD (drug/emollients/traditional Chinese medication/Ultraviolet [UV] therapy) during maintenance phase, (vi) Quality of life (QoL) assessed by validated questionnaires. Questionnaire was selected based on patient's age: The Infants' Dermatitis Quality of Life Index (IDQOL) (<4 years), Children's Dermatology Life Quality Index (CDLQI) (4 −16 years) and Dermatology Life Quality Index (DLQI) (≥17 years), (vii) time to flare and the number of flares during the maintenance period (viii) AD symptoms of the face assessed for patients 18 years and above using a modified sensitive scale (SS) −10 questionnaire and (ix) PIM safety and tolerability (adverse drug reactions and special situations) during the whole study period.

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Statistical Methods

Sample Size Determination

The primary endpoint of this study was the change in SCORAD index from inclusion to Visit 2. It was expected that the PIM treatment effect was higher than the minimal clinically relevant difference of 8.7 and standard deviation of the pre-post difference values was not higher than 25. With 90% power, this led to a sample size of 89 completers (pre- and post-assessment). To account for a substantial number of dropouts without post assessment, it was planned to include 130 patients in the study.

Statistical Analysis

Descriptive statistics for demographics and baseline characteristics, efficacy endpoints, and safety parameters were presented. Continuous variables were described by number, mean, standard deviation, minimum, median, and maximum. Analysis of covariance was used to analyse the change from inclusion SCORAD index to Visit 2 using baseline (inclusion time point) as covariate and the change from baseline to Visit 2 as a dependent variable. Itching score was measured by Visual Analog Score (VAS) which was analysed by using Wilcoxon sign-ranked test.

Ethics

The study was reviewed and approved by institutional review boards (IRBs) at participating sites. The ethics number of leading site (Peking University Third Hospital) was 2020–293-02. Patients provided written informed consent/paediatric assent. If the patient was a minor, a parent or legal guardian must have given written informed consent. The study followed all the applicable laws and guidelines; International Conference on Harmonization (ICH)/Good Clinical Practices (GCP), in accordance with the principles of the Declaration of Helsinki, and with US Code of Federal Regulations (CFR).

Results

Patient Disposition and Demographics

A total of 130 patients were screened into the study, of which 128 (100.0%) were confirmed by the investigators and prescribed PIM. A total of 110 (85.9%) patients completed the study. Among 18 (14.1%) patients who did not complete the study 15 (11.7%) withdrew consent and 3 (2.3%) were lost to follow-up. Disposition of all enrolled patients is summarized in Table 1. The mean (SD) age of patients was 20.1 (16.51) years with mean (SD) age of 3.3 (2.78) years for patients below 13 years and 33.3 (11.99) years for those above 13 years. In this study, 48 (37.5%) were male and the remaining 80 (62.5%) patients were females. The mean (SD) of duration of AD was 3.7 (4.32) years. Of the 128 enrolled patients, 37 (28.9%) patients had essential historical features of AD at an early age (<2 years); 37 (28.9%) patients had personal or family history of AD; 74 (57.8%) patients had mild AD and 54 (42.2%) patients had moderate AD in the past. None of the patients had severe AD in the past. All 128 patients in the study reported to have symptoms, of which 117 (91.4%) patients had symptom of itching, 114 (89.1%) had symptoms of redness, 109 (85.2%) had dryness, 49 (38.3%) had sleep disturbance, 42 (32.8%) patients had desquamation, 9 (7.0%) patients had sleep loss, and 1 (0.8%) patient had other symptoms. The sensitive skin area affected by AD in patients with age >12 years were face in 34 (50.7%), followed by anogenital area in 21 (31.3%), neck in 18 (26.9%), and intertriginous area in 15 (22.4%) patients. The sensitive skin area affected by AD in patients with age ≤12 years were neck in 20 (62.5%), face in 16 (50.0%), followed by intertriginous area in 11 (34.4%), and anogenital area in 5 (15.6%) patients.

Primary Efficacy Analysis

The mean (SD) baseline of SCORAD index was 25.9 (8.5) (Table 1). The mean (SD) SCORAD index at visit 2 was 10.1 (10.73) [median (Q1:Q3) - 7.2 (0:15.6); min: max - 0: 52.2]. The primary analysis showed a significant reduction in the SCORAD index from baseline at both visit 2 ($P < 0.0001$) and visit 3 ($P < 0.0001$) in both age- groups (Figure 2A). The mean change in SCORAD index (SD) from baseline at visit 2 and visit 3 was −15.4 (10.50) and −18.6 (11.57), respectively.

Table 1 Patient Disposition

Disposition	**Overall (N=128)**
Screened	130
Data confirmed by the investigator and prescribed PIM (safety population) [n(%)]	128 (100.0%)
Patients completed the study [n(%)]	
Yes	110 (85.9%)
No	18 (14.1%)
If No, Reason for discontinuation [n(%)]	
Withdrawal by Patient	15 (11.7%)
Adverse Drug Reaction	0 (0.0%)
Investigators Decision	0 (0.0%)
Lost to follow up	3 (2.3%)
Age [mean (S.D)] years	20.1 (16.51)
Gender [n(%)]	
Male	48 (37.5%)
Female	80 (62.5%)
Areas affected by AD (age >12 years) [n(%)]	
Face	34 (50.7%)
Anogenital area	21 (31.3%)
Neck	18 (26.9%)
Intertriginous area	15 (22.4%)
Areas affected by AD (age ≤12 years) [n(%)]	
Face	16 (50.0%)
Anogenital area	5 (15.6%)
Neck	20 (62.5%)
Intertriginous area	11 (34.4%)
SCORAD Index (baseline)	
Mean (SD)	25.9 (8.5)
Median (Q1:Q3)	24.5 (18.9: 31.9)
Min:max	10:46.7

The mean baseline SCORAD index (SD) was 27.4 (8.2) and 24.6 (8.6) for age groups 2–12 years and ≥12 years respectively and mean change in SCORAD index from baseline at visit 2 was −15.4 (12.06) and −15.4 (9.26) for age groups 2–12 years and ≥12 years, respectively. At the end of the study (visit 3), the mean change in SCORAD index was −18.2 (11.7) and −18.9 (11.56) for age groups 2–12 years and ≥12 years, respectively (Figure 3A).

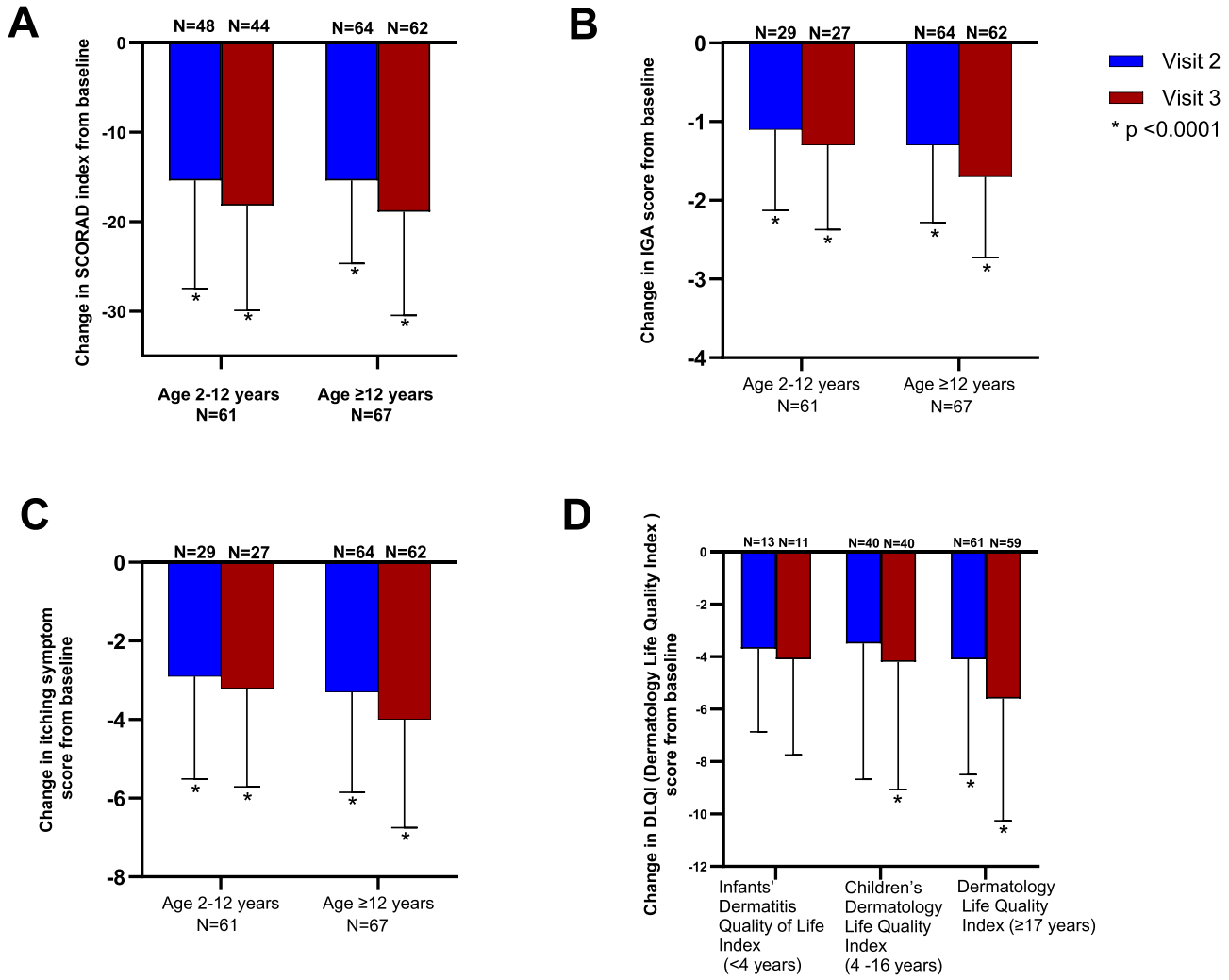

Figure 2 (**A**) Change in SCORAD index from baseline in two study groups, (**B**) Change in IGA score from baseline in two study groups, (**C**) Change in itching symptom score from baseline in two study groups and (**D**) Change in Quality-of-life Index – Safety Population (N=128) (* p <0.0001).

Secondary Efficacy Analysis

Reduction of AD in Sensitive Skin Areas Assessed by IGA

The improvement in signs and symptoms of AD were evaluated by IGA score at each visit (Figure 2B). The mean IGA score progressively decreased from Visit 1 (Baseline) to Visit 3 (EOS) (Figure 3B). The mean (SD) IGA score at Visit 1 (Baseline) was 2.3 (0.56); at Visit 2 (EOT) was 1.0 (0.97); and at Visit 3 (EOS) was 0.7 (0.94). The mean (SD) changes in IGA score from Visit 1 (Baseline) to Visit 2 (EOT) was −1.2 (1.00) which was statistically significant ($P < 0.0001$). Similarly, the mean (SD) changes in IGA score from Visit 1 (Baseline) to Visit 3 (end of study) was −1.6 (1.05) which was statistically significant ($P < 0.0001$).

Itching Symptoms in Sensitive Skin Areas

The mean itching score progressively reduced from Visit 1 (Baseline) to Visit 3 (EOS) (Figure 2C). The mean (SD) itching score at Visit 1 (Baseline) was 4.7 (2.49); at Visit 2 (EOT) was 1.6 (2.07); and at Visit 3 (EOS) was 0.9 (1.71). The mean (SD) changes in itching symptoms from Visit 1 (Baseline) to Visit 2 (EOT) was −3.1 (2.56). Similarly, the mean (SD) changes in itching score from Visit 1 (Baseline) to Visit 3 (EOS) was −3.7 (2.69). There was significant ($p<0.0001$) reduction in the itching scores from Visit 1 to Visit 2 and from Visit 1 to Visit 3 (Figure 3C).

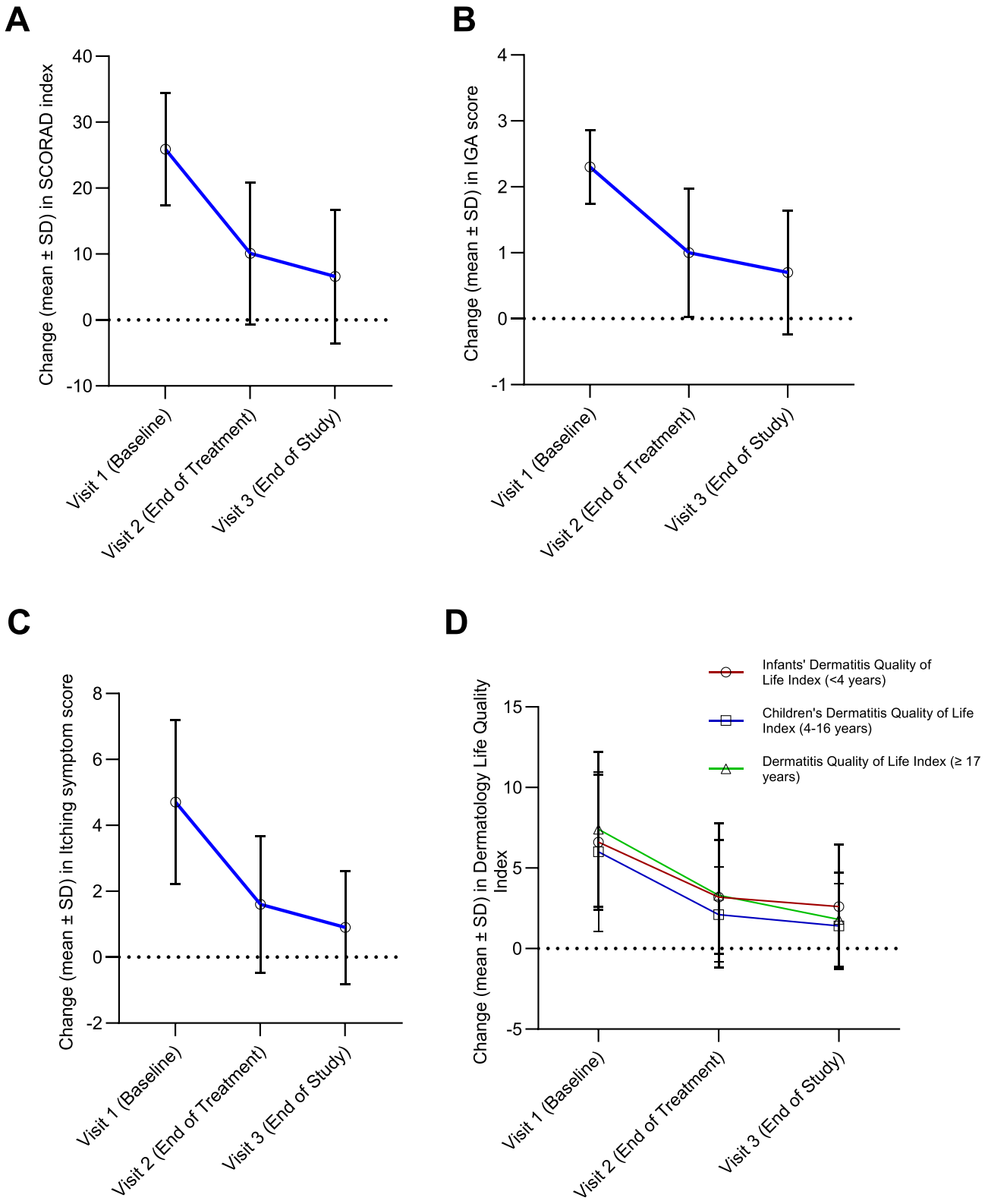

Figure 3 (**A**) Change in SCORAD index, (**B**) Change in IGA score, (**C**) Change in itching symptom score and (**D**) Change in Quality-of-life Index – Safety Population (N=128) at each visit (* p <0.0001).

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Table 2 Summary of Questionnaires/Symptom Assessment for Face Among Patients >18 years – Safety Population (N=128)

Visit	N	Mean	Standard Deviation (S.D)
Visit 1 (Baseline)			
Daytime symptom	43	8.7	8.67
Nighttime symptom		8.0	9.31
Visit 2 (EOT)			
Daytime symptom	40	1.5	3.78
Nighttime symptom		1.3	3.91
Visit 3 (EOS)			
Daytime symptom	37	1.6	3.99
Nighttime symptom		1.5	4.11

Treatment Duration

Of the 114 patients at Visit 2 (EOT), 112 (98.2%) patients received PIM treatment as per physician prescription, 102 (89.5%) patients received PIM treatment every day. Overall, the mean (SD) duration of PIM use was for 38.3 (2.34) days. Similarly, the mean (SD) duration of PIM use was 36.9 (3.01) days for patients with AD with sensitive skin affected (>12 years) and 40.2 (3.72) days for patients with AD (<=12 years). Additionally, patients with mild AD (SCORAD index <25) had a mean (SD) treatment duration of 38.2 (3.32) days, and those with moderate AD (SCORAD index 25–30) had a duration of 38.6 (3.32) days.

Use of Treatments for AD During Maintenance Period

A total of 47 patients (36.7%) were taking additional AD treatments that had been prescribed during the maintenance phase at visit 3. Of these, 37 (28.9%) used moisturizers or emollients; 10 (7.8%) took topical corticosteroids; 3 (2.3%) took PIM and antihistamines; 2 (1.6%) took tacrolimus and other topical therapies; and 1 (0.8%) took systemic immunosuppressant, systemic corticosteroids, systemic antimicrobials, and traditional Chinese medicine, respectively.

Quality of Life Assessed by Validated Questionnaires

The mean (SD) DLQI score progressively reduced from Visit 1 (Baseline) to Visit 3 (EOS). Similar results were observed in the IDQOL and CDLQI. The baseline scores for IDQOL, CDLQI and DLQI is 6.6 (4.2), 6.0 (4.94) and 7.4 (4.81), respectively. Change in IDQOL, CDLQI and DLQI from baseline at visit 2 was −3.70 (3.17), −3.50 (5.18) and −4.10 (4.40), respectively (mean days after baseline 38.3, all $p < 0.01$). Change from baseline in IDQOL, CDLQI and DLQI at visit 3 was −4.10 (3.65), −4.20 (4.86) and −5.60 (4.66), respectively (mean days after baseline 159, all $p < 0.01$) (Figure 2D). The published estimate of the minimal clinically important difference of 3.3 for the DLQI score for each age group was reached.

Number of Flares

Sixty-one (47.7%) patients had a flare in the maintenance phase of the study after treatment. The mean time to first flare (available for 57 patients) was 89.4 days and median time to first flare was 100 days. A total of 47 (36.7%) patients had 1–2 flares, 7 (5.5%) patients had 3–4 flares, and 7 (5.5%) patients had >4 flares during maintenance phase.

AD Symptoms of the Face Assessed for Patients >18 years Using a Modified SS-10 Questionnaire

The mean modified SS-10 scores at baseline, visit 2 and visit 3 are listed in Table 2.

Safety

There were no ADRs, or other significant AEs reported during the whole study period.

Discussion

The current NIS gathered knowledge on the actual use and effectiveness of PIM in Chinese patients with mild-to-moderate Atopic Dermatitis affecting sensitive skin areas in routine clinical practice. The study demonstrated the efficacy of PIM by reducing the severity of AD by 71.8%. The overall change in the mean SCORAD index was higher than the minimal clinically important difference (MCID) reported for SCORAD index.[16] The efficacy results observed in this study are consistent with the other previously conducted controlled clinical studies and those reflecting from clinical practice.[14,17–20] In a double-blind study, the effect of PIM cream on different standard eczema scores was analysed in infants with AD. PIM (n = 129) or vehicle control (n = 66) was administered for 4 weeks. Following treatment with PIM, the mean SCORAD, IGA and Eczema Area and Severity Index (EASI) had significantly reduced on Day 29 as compared to vehicle group ($P = 0.002$, $P < 0.001$, $P < 0.0001$, respectively). The mean percentage change from baseline in SCORAD Index was –55.2% for the PIM group compared to +1.13% for the vehicle group.[21]

There was significant reduction in the signs and symptoms of AD in sensitive skin areas assessed by IGA and the itching scores at Visit 2 and Visit 3 ($p < 0.0001$). A sub-group analysis of the PETITE study in the Chinese population showed that there was a progressive increase in facial IGA treatment success, in patients treated with PIM with the overall facial IGA treatment success at year 5 for PIM was 100% while for TCS it was 97.8%.[15] A recent meta-analysis showed that PIM was more efficacious than vehicle in achieving IGA 0/1 up to week 6 in children and in patients with AD of sensitive skin areas with a comparable safety profile.[22] The present study reports a positive impact of PIM on IDQL (<4 years) and CDQL (from 4 to 16 years). This is consistent with previous studies which show significant improvement in the quality-of-life scores in both children and adults with PIM.[23,24] Few adverse events (nasopharyngitis, pyrexia, diarrhoea, upper respiratory tract infection and cough) were reported in the sub-group analysis of the PETITE study in the Chinese sub-population with similar incidence in both PIM and TCS groups.[15] The small number of dropouts and the absence of any adverse drug reaction in the current study suggests that PIM is well tolerated among the patients with AD particularly in sensitive skin areas. These results collectively support the current European guidelines recommendation to use TCI for treating AD in children and areas of sensitive skin.

The present analysis showed that PIM is effective in controlling the recurrence of flares by providing a flare free period up to 100 days in paediatric and adult Chinese patients with mild-to-moderate AD. Notably, only 7.8% of the patients used TCS till the end of study (visit 3) indicating a TCS sparing effect of PIM. In a study with 192 adults with mild-to-moderate AD, the median time to first flare was 144 days in the PIM group and 26 days in the control group. Additionally, PIM group used corticosteroids on 14.2% of days compared to 37.2% in the control group. Given the association of TCS with Corticophobia, adverse events, misuse, and the unsuitability for long-term treatment, there is a need for alternative approaches. Recently, experts in China have recommended a TCS-sparing strategy, highlighting the role of topical calcineurin inhibitors (TCIs), particularly PIM 1% cream, in managing patients with mild-to-moderate - AD.[2]

Limitations of the Study

Non-interventional studies (NIS) are crucial for understanding real-world outcomes and patient behaviours. While NIS can provide valuable insights into treatment practices and patient characteristics, the observational nature of these studies can introduce biases in participant selection and data collection, potentially affecting the validity of the findings. Additionally, without randomization or intervention, these studies may not adequately control for confounding factors, which can skew results.[25]

Conclusions

This study provides robust real-world evidence that PIM 1% cream is effective for the treatment of mild-to-moderate AD in Chinese patients, particularly in sensitive skin areas and paediatric population. PIM also offers a TCS-sparing approach, making it a valuable option for managing mild-to-moderate AD.

Statement of Ethics

The study was reviewed and approved by institutional review boards (IRBs) at participating sites. The ethics number of leading site (Peking University Third Hospital) was 2020-293-02. Patients provided written informed consent/paediatric assent. If the patient was a minor, a parent or legal guardian must have given written informed consent. The study followed all the applicable laws and guidelines; International Conference on Harmonization (ICH)/Good Clinical Practices (GCP), in accordance with the principles of the Declaration of Helsinki, and with US Code of Federal Regulations (CFR).

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Disclosure

All authors declare no conflicts of interest associated with the publication of this study.

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