

Case Series

Atopic dermatitis and role of Relizema: a multi-country user experience

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ABSTRACT

Atopic dermatitis (AD) is characterized by itching or pruritus, erythematous lesions, pruritus, and a skin barrier defect. Repeated scratching can trigger the itch-scratch cycle. Itching is associated with an adverse impact on quality of life. The first-line treatment of AD includes the use of topical corticosteroids for atopic dermatitis. However, parents of children with atopic dermatitis are often reluctant to accept the use of topical corticosteroids due to their concern of adverse effects flare-up. Relizema™ cream is a prescription emollient device (PED) multi-ingredients moisturizer formulation that has been indicated for the treatment of signs and symptoms of dermatitis. It is approved as medical device (MD) class IIa in Europe and it is registered as a topical medical device in countries of Asia Pacific. A consensus meeting of 9 dermatologists from multiple countries in Asia Pacific region treating atopic dermatitis was conducted. The dermatologists presented their cases of atopic dermatitis. PED was reported by patients to offer good relief of symptoms and improve skin softness unlike other moisturizers. In fact, a few patients reported relief with Relizema™ cream after using other moisturizers which were not demonstrating clinical effectiveness. Patients reported they noticed a softness in their skin after the application of the PED. PED was effective even in patients with lichenified skin. The formulation which is enriched with antioxidants helped relieve eczema. Due to its steroid-free formulation, the PED can be continued as a part of long-term maintenance treatment to maintain healthy skin conditions, prolong remission, and prevent recurrence.

Keywords: Atopic dermatitis, Relizema™ cream, Prescription emollient device

INTRODUCTION

The skin is one of the primary protective barriers for the

underlying tissues from infection, desiccation, chemicals, and mechanical stress. Disturbance in the skin barrier causes increased trans-epidermal water loss leading to

conditions like atopic dermatitis and other chronic skin diseases.¹

Atopic dermatitis (AD), or atopic eczema (AE), is a chronic relapsing and remitting inflammatory skin condition with a lifetime prevalence of about 10%.² The onset of atopic dermatitis commonly occurs between the ages of 3 and 6 months up to the age of 5 years, but it can occur at any age.^{3,4} About 16.8% of adults with AD present with symptoms of atopic dermatitis after adolescence.⁵⁻⁷ Atopic dermatitis occurs more frequently in Asian and Black individuals than Whites. The risk factors implicated in the development of AD include a family history of atopic disease.^{3,8} A maternal history that may be more predictive for AD.^{9,10}

AD is characterized by itching or pruritus, erythematous lesions, pruritus, and a skin barrier defect.¹¹ Repeated scratching can trigger the itch-scratch cycle. Itching is associated with an adverse impact on quality of life.¹² About 36% of patients have reported that their primary treatment goal is decreasing the amount of itch.¹³ Emotional stress increases itching, and may be indicative of a bidirectional relationship.¹⁴ Itching causes sleep disturbances in about two-thirds of patients with AD leading to daytime fatigue.^{15,16}

AD is also associated with work and school absenteeism, and results in decreased productivity and decreased quality of life.^{12,17-20} Children with AD may have an increased risk of developing attention-deficit/hyperactivity disorder, headaches.²¹⁻²³ In adults, AD is associated with reduced self-esteem and a negative impact on social life.^{24,25}

The suffering of the child of atopic dermatitis also has a negative impact on about 30% of parents and caregivers.^{9,25} The two theories proposed to explain AD are the inside-out and outside-in hypotheses.^{22,23,26} As per the inside-out hypothesis, it is postulated that allergic triggering weakens the skin barrier that furthers facilitates allergen introduction and presentation.^{22,23} This indicates that inflammation is primarily responsible for impaired skin barrier, resulting in increased penetration of allergens and microbes. On the contrary, the outside-in hypothesis, postulates that the impaired skin barrier precedes AD and is the prime factor responsible for immune dysregulation.^{22,23}

The first-line treatment of AD includes the use of topical corticosteroids for atopic dermatitis. But, parents of children with atopic dermatitis are often reluctant to accept the use of topical corticosteroids due to their concern of adverse effects flare-up.²⁷

Topical calcineurin inhibitors such as pimecrolimus and tacrolimus can also be used in conjunction with topical corticosteroids as first-line treatment. Anti-staphylococcal antibiotics may be prescribed for treating secondary skin infections. Oral antihistamines are not recommended as they may reduce pruritus.²

The novel steroid-free treatment option in atopic dermatitis

Relizema™ cream is a prescription emollient device (PED) multi-ingredients moisturizer formulation that has been indicated for the treatment of signs and symptoms of dermatitis. It is approved as medical device (MD) class IIa in Europe and it is registered as a topical medical device in countries of Asia Pacific. This MD classification ensures its level of evidence-based medicine (EBM) as compared to cosmeceuticals emollients and or generic moisturizers. Its formula with several key ingredients has an important role to address the multi-pathogenesis factors of AD and in relieving the symptoms of atopic dermatitis. Offering physicians and patients a valid treatment option of a non-steroidal (steroid-free) effective and well-tolerated management of AD, that can be used as monotherapy or in combination with standard drugs, a valuable armamentarium especially for those who are steroid-phobia.²⁸

Expert consensus in atopic dermatitis management

A consensus meeting of 9 dermatologists from multiple countries in Asia Pacific region (Indonesia, Malaysia, Singapore, Philippines, Hong Kong, and Thailand) treating atopic dermatitis was conducted. The dermatologists presented their cases of atopic dermatitis and their approach to treatment. Discussions followed the case presentations of various clinical-presentation of atopic dermatitis and the role of Relizema™ cream (PED) in the treatment.

CASE SERIES

Case 1

A 23-year-old female presented with a history of atopic dermatitis since childhood. She had recent worsening with secondary infection. The lower limbs were the dominant areas of involvement. Her ankles are were lichenified (Figure 1a).

She was treated with mometasone furoate ointment since betamethasone dipropionate cream was not effective. Moisturizer on one leg. PED cream was added to the treatment protocol for one leg while for the other leg she continued to use the moisturizer on the other leg. Symptoms resolution occurred with Relizema™ (Figure 1b) Subsequently, the patient preferred to use PED cream on the other leg too. She stopped using mometasone ointment due to concerns of it being a corticosteroid.

Case 2

A 26-year-old male who was a known patient of atopic dermatitis since the age of 13 years.

Presented with predominant involvement of the hands and feet involvement. He had been well controlled for many

years before his relapse episode of eczema. He had large patches of eczema on both scapulae and posterior waistline extending to buttocks across lower abdomen. Mild patches were seen on the lateral chest, inner arms, forearms and thighs (Figure 2a).

He was advised betamethasone valerate 0.1% cream twice daily, oral bilaxten 20 mg morning and 40 mg at night. PED was prescribed as a twice daily application. Eczema improved after 3 days of application of topical corticosteroid. He did not continue its use. The use of PED together with topical corticosteroid helped a rapid improvement of eczema. PED had a steroid sparing effect (Figure 2b).

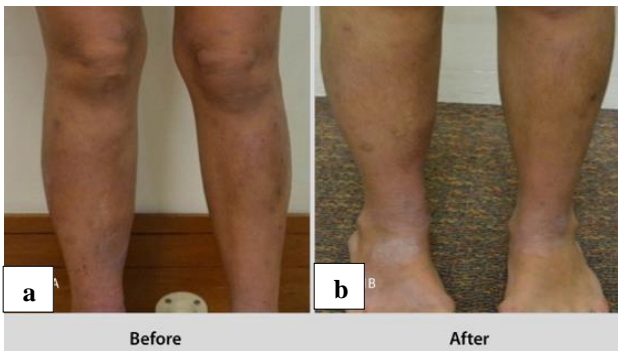


Figure 1: Patients with (a) atopic dermatitis related lichenified ankles and (b) resolution after PED.

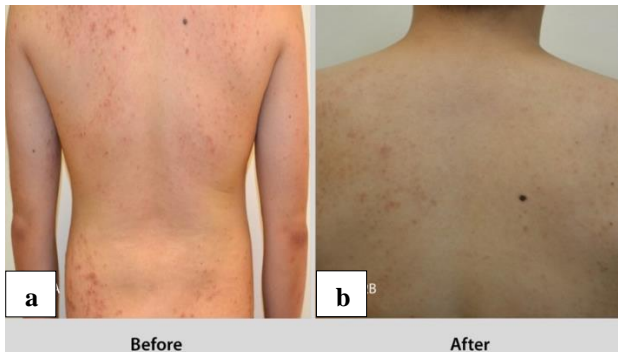


Figure 2: Patients with large patches of eczema on both scapulae (a) posterior waistline extending to buttocks and (b) resolution after treatment.

Case 3

A 37-year-old female presented with bilateral periorbital rash for 2 weeks, with marked itching (Figure 3a). She had recurrent eczema at all flexural and periorbital areas every other month.

She was treated with topical corticosteroid, topical calcineurin inhibitor, and sometimes short course of oral prednisolone. PED application for 2 weeks was advised and oral antihistaminic. The rash and itchy symptom was significantly improved in 2 weeks. The patient was very satisfied with the treatment. As compared to topical

calcineurin inhibitor PED caused minimal less burning and stinging sensation. The periorbital skin after the treatment was markedly soft and moisturized (Figure 3b).



Figure 3: Eczema in the (a) periorbital areas and (b) resolution after treatment.

Case 4

A 22-year-old male had atopic dermatitis and mild intermittent allergic rhinitis since the age of 10, had recurrent, pruritic maculopapular rashes on the face, flexural areas on and off for 12 years (started age 10) (Figure 4a). Lesions were weepy/eczematous during acute flares. Some would progress to lichenified plaques (usually on the legs). The flares had increased in severity and frequency over the past 2 years. He had a family history of atopy.

He was treated with treated with potent topical corticosteroids potent for 2 weeks, then proactive treatment. He was also prescribed antihistamine drugs for 1 month, methotrexate in a tapering dose over 3 months. Relizema™ cleanser, cream and lotion twice daily application was also recommended. The patient had significant improvement of symptoms by day 7. The flares responded to the regimen of topical steroids, oral antihistamines, methotrexate, and PED. The PED helped to restore the moisture of the skin, it shortened the duration of steroid treatment, greatly decreased the pruritus (Figure 4b).



Figure 4: Patient with pruritic maculopapular rashes on the face, (a) flexural areas and (b) resolution after treatment with PED.

Case 5

A 20-year-old female nurse had been diagnosed with atopic dermatitis since childhood. During COVID-19 pandemic, she suffered from recurrent attacks caused by stress, night-shift and frequent hand washing and frequent use of an alcohol-based sanitizer. Currently, she had erythematous itchy swelling with vesicular discharge and crusts over both hands, symmetrical dry scaly cracks and rash over both palm (Figure 5a). Blood culture indicated the presence of *Staphylococcus aureus* and the potassium hydroxide (KOH) fungal test was negative.

In the past she used topical corticosteroids like mometasone 1% cream occasionally klacid 250 mg BD po, betamethasone ointment topical. PED liberal use after hand washing if possible. She responded well to PED (Figure 5b).



Figure 5: (a) Atopic dermatitis of hands and (b) resolution after treatment.

Case 6

A 30-year-old lady presented with itchy rash since childhood (Figure 6a). It had a waxing and waning course and affected her social activities. She also had episodes of bacterial infection.

She was treated with dupilumab and regular use of PED. The treatment was well tolerated. She had no stinging even on excoriated sites. The patient previously did not tolerate other moisturizers because of stinging (Figure 6b).

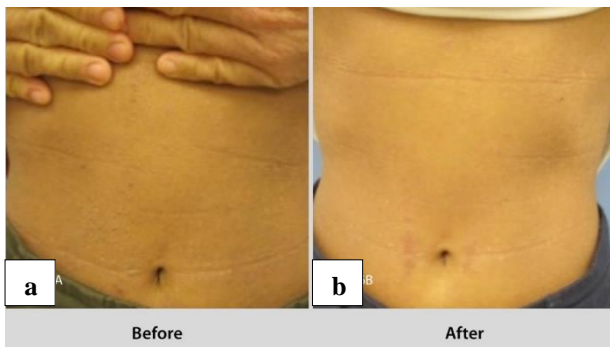


Figure 6: (a) Itchy rash related to atopic dermatitis and (b) resolution post treatment with PED.

Real-world clinical evidence in children

Case 1

A 6-year-old boy presented with forehead and flexural eczema for 3.5 years. 10 weeks ago, he had a flare up of the eczema. His parents are steroid phobic.

He was treated with desonide twice daily for 4 weeks, followed by desonide once daily for 2 weeks, PED 3 times per day on left side of forehead. Olive oil application was advised on right side of forehead.

80% improvement was observed with the combination therapy over 1 weeks. PED has a steroid sparing effect. The patient was happy with PED and preferred to stop the olive oil applied on right side and shifted to PED. No adverse effects were observed.

Case 2

A 8 month old girl was brought with erythematous plaque with scales on right nipple and areola of 3 months duration (Figure 7a). There was moderate pruritus, oozing and crusting. She had a positive family history of atopy.

Application of topical corticosteroid helped resolve the symptoms completely, but on discontinuation a relapse occurred. BID application of PED daily as maintenance regimen. Subsequently she had complete resolution of symptoms and no recurrence (Figure 7b).

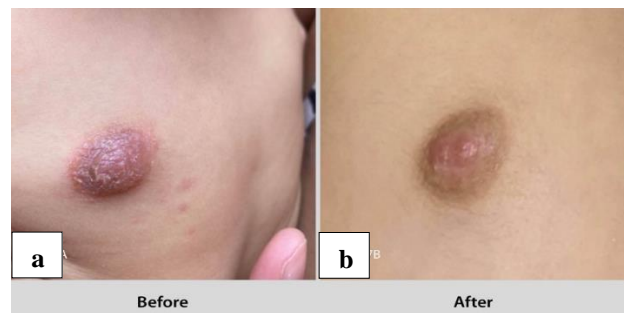


Figure 7: (a) Erythematous plaque with scales on right nipple and (b) resolution after treatment with PED.

Case 3

3.5 months old baby boy was brought by his parents who were concerned about the mild rash on both cheeks, slight erythema, dry skin for 3 weeks. PED application twice a day was advised. There was significant improvement in the erythema and dry skin.

Case 4

5-year-old girl presented with itchy rash of moderate grade on the face, inside of elbow fold of for one month. Her symptoms had a waxing and waning pattern.

She was treated with PED topical application twice a day. By week 3 relief of pruritus and erythema was observed.

Case 5

A 2 year old boy was brought with complaints of itchy rash on the face and flexor surfaces diagnosed as atopic dermatitis since the past 1 year with a waxing and waning course (Figure 8a). He also had episodes with bacterial infection.

He was treated with antibiotics for the bacterial infection. PED topical application twice a day. PED was well tolerated, with no stinging even on excoriated sites (Figure 8b).

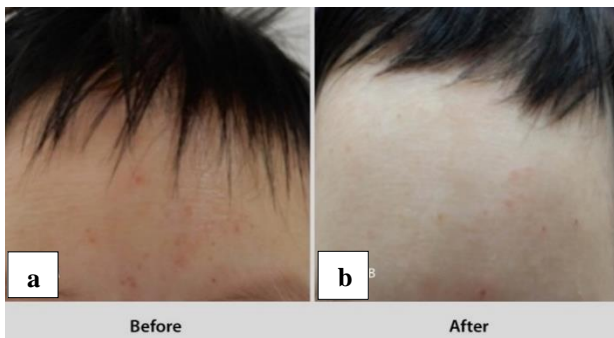


Figure 8: (a) Itchy rash on the face and flexor surfaces and (b) resolution after PED treatment.

Case 6

A 12-year-old girl presented with complaints of itching, and redness in the face, neck and both palms (Figure 9a). She has atopic dermatitis since she was 2 months old with a waxing and waning course. She also has severe allergic rhinitis over the past 3 months. Her vitamin D levels were low (7 ng/μl). She was treated with montelukast 10 mg per day, vitamin D 2000 IU per day and the antihistaminic drug cetirizine when needed. PED application was prescribed 2 times a day after bath or more if needed. After 2 weeks, the patient felt better, pruritus was reduced slight and showed slight erythema. PED reduced the skin dryness and itchiness (Figure 9b).



Figure 9: (a) Atopic dermatitis related itching, and redness in the face, neck and (b) resolution after treatment with PED.

DISCUSSION

Scientific evidence on the efficacy of Relizema™ cream in the management of atopic dermatitis

Our current knowledge about AD pathogenesis is based on the concepts of barrier dysfunction, pruritus/inflammation, and a dysfunctional immune response. Oxidative stress is considered to play a central role in the pathogenesis of AD. The release of reactive oxygen species, directly damages the skin's cellular components, such as the DNA, the cell membrane, and the organelles. Hence, oxidative stress may be another potential target in AD management. Alternative pharmaceutical antioxidant agents, such as furfuryl palmitate and its derivatives, can be considered to offer effective and safe steroid-sparing effects in AD in the future. But robust trials are required needed to demonstrate the benefits of these agents for the prevention and treatment exacerbations of AD.²⁹

Relizema™ cream is the novel PED formulated with several ingredients which have a synergistic effect in atopic dermatitis, uniquely the PED is enriched with antioxidant (furfuryl palmitate and tocopherol/vitamin E). The furfuryl palmitate brings a significant improvement in cutaneous inflammation, with evident, rapid reduction of the inflammation and soothing effects. The glycerine contained is well known as a skin moisturizer and humectant agent. The tocopherol (vitamin E) is a lipophilic antioxidant that serves as a protective agent for the cell membrane and the stratum corneum. The hydrogenated polyethylene and ethylhexyl palmitate are emollients and skin-conditioning agents. Dimethicone is a polymer of silicon and oxygen that works as an effective occlusive. The *Ricinus communis* seed oil is an emollient and a skin-conditioning/occlusive agent. The Vitamin F Ethyl Ester acts as emollient agent, Vitamin F is better known as linoleic acid, an omega-6 essential fatty acid (EFA). In skincare, linoleic acid provides moisturizing and healing support. Linolenic acid acts as a skin conditioning agent and surfactant-cleansing agent. Due to the above essential ingredients, PED creates a sheer physical barrier that separates the skin from the surrounding environment, useful for generating favourable conditions for the maintenance and/or recovery of the physiological cutaneous layer in case of dermatitis. It improves dry skin by keeping it hydrated.² Due to its derma-protective action it helps maintain and restore the physiological skin barrier. Its formulation protects and moisturizes the skin with a soothing effect.

In a recent an open-label uncontrolled trial conducted at the dermatology department of the University Hospital of Modena, Modena, Italy, Pellacani et al showed clinical results following the use of Relizema™ cream (RELIFE S. R. L. Menarini group, Firenze, Italy; marketed formulation) by a group of 40 adult patients with mild-to-moderate AD or CD. In this study, after 28 days' twice-daily administration, statistically, significant reductions were observed in the primary endpoint, investigator global

assessment (IGA) scores (rated on a 0-4 scale, where 4 is 'severe'), from the baseline, mean score reflecting mild-to-moderate disease, to a mean score of 'almost-clear-to-mild' at day 14, and 'almost-clear' at day 28. Similar improvements were observed at days 14 and 28 on the secondary endpoints, including eczema severity [as calculated with the eczema area and severity index (EASI)] and pruritus intensity (as evaluated with a visual analogical score). Patients also reported a statistically significant improvement in quality of life at the end of the trial [as evaluated with the dermatology life quality index (DLQI)]. Overall, the skin condition improved in over 90% of patients on both investigator-rated and patient-rated assessments. No safety issues were identified and most patients were satisfied with the product characteristics and ease of use.³⁰

The clinical evidence-based paradigm across age groups

PED was found to be effective and safe across age groups (2 months onwards) in infants, children, adolescents, and adults. No gender differences were observed in clinical performance and treatment outcome. Since there is no age limit to the use of Relizema™ cream, these real-world multi-countries clinical evidence confirm its effectiveness and tolerability when used in infants as young as a few months old.

The clinical evidence-based paradigm in relieving symptoms

PED was reported to relieve symptoms such as itching significantly. In general, a rapid clinical symptoms relief has been reported as early as day 3 after application. The rash, itching was reported to be relieved significantly at follow-up visits by all patients. Thanks to its function in helping the restoration of normal skin barrier function, it helped relieve itching associated with exacerbations or flare-ups, reduced scaling, erythema, pruritus. From our observation, PED helps reduce recurrences and relapses, which open the opportunity to investigate through larger cohort clinical studies.

The clinical evidence-based paradigm on effectiveness in spite of the presence of risk factors of atopic dermatitis present in the patients

PED was observed to offer effective and significant relief of symptoms in patients with evident risk factors such as family history of atopy, exposure to the hot tropical climate, stressors like examinations, and following the frequent hand washing in medical and paramedical personnel or in times of COVID-19 pandemic.

The clinical evidence-based paradigm on the use in skin areas where topical corticosteroids cannot be used

One case of periorbital atopic dermatitis rash in the periorbital area was presented. PED application for two weeks leads to a significant reduction in itching and rash

in the periorbital area. The patient reported no stinging sensation. The periorbital skin was soft and moisturized. It offers a valuable treatment option especially for the use in the sensitive regions like the like facial, periorbital, and genital areas effectively and with well-tolerability.

The clinical evidence-based paradigm on the steroid-sparing effect

Early relief of symptoms of atopic dermatitis with the application of PED, helps patients to taper off steroid application early in the course of treatment. The panelists opined that topical corticosteroid may be used along with PED for a short period if required to offer rapid relief or symptom reduction of the pruritus. Then the topical corticosteroids can be stopped and PED can be continued. A valuable combination of treatment modalities between standard drugs (topical corticosteroids or topical calcineurin inhibitors) and an effective steroid-free PED for the benefit of our patients.

The clinical evidence-based paradigm in steroid phobia

Compliance to topical corticosteroids is poor especially in children whose parents are concerned about the side effects of corticosteroids. PED is a scientifically rational treatment option to help overcome the issue of steroid phobia and play an important role in the management of atopic dermatitis patients with eczema. After the treatment with the PED, patients reported satisfaction toward the symptom's relief, clinical performance, and were not associated with a stinging sensation, unlike other moisturizers.

The clinical evidence-based paradigm of better symptom relief than other moisturizers

PED was reported by patients to offer good relief of symptoms and improve skin softness unlike other moisturizers. In fact, a few patients reported relief with Relizema™ cream after using other moisturizers which were not demonstrating clinical effectiveness. Patients reported they had observed a softness in their skin after the application of the PED.

PED was effective even in patients with lichenified skin. The formulation which is enriched with antioxidants helped relieve eczema. Due to its steroid-free formulation, the PED can be continued as a part of long-term maintenance treatment to maintain healthy skin conditions, prolong remission, and prevent recurrence.

Good patient compliance for Relizema™ cream

Patients have reported no or minimal stinging sensation after application of PED cream. Patients have liked the texture of the PED, as it's not oily or messy, even in the hot tropical climates. In humid climate, patients have reported that with other products' oily formulations, they find that after application, it mixes with sweat and leads to

a peculiar body odour. But this issue was not observed with PED.

CONCLUSION

The prevalence of atopic dermatitis is rising. The burden posed by AD has a significant impact on not only the patients but also on their families. AD can have an adverse impact on their quality of life. The reluctance of patients to use topical corticosteroids and the steroid phobia of parents of children with atopic dermatitis poses a challenge to the use of topical corticosteroids. Secondly, the stinging sensation is caused by the available moisturizers. Relizema™ cream is a novel PED specially formulated to overcome the issues posed by the available moisturizers. It offers rapid and effective symptom relief in patients with AD. Relizema™ cream can have a place in the maintenance phase of AD and can help prevent relapses. It improves the clinical condition of AD patients, improving skin texture even in patients with eczema, most importantly clinically proven effective and well-tolerated in infants, children, adolescents, and adults. It is noted that most patients providing feedback that they prefer Relizema™ cream to other moisturizers due to the absence or minimal stinging. Relizema™ cream can have a major role to play in the management of atopic dermatitis across all ages, can be used as monotherapy or in combination with standard topical drugs (to reduce and manage the risk of side effects of drugs application). Finally, a new hope for a better quality of life for patients with AD.

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