Pruleva™
Easy Cream

A NON STEROIDAL IMMUNO-MODULATORY TOPICAL CREAM FOR SAFE & LONG TERM TREATMENT OF MODERATE TO SEVERE REFRACTORY ATOPIC DERMATITIS (AD) IN ADULTS & CHILDREN

Bernard Low (PhD Nursing)
Chief Scientific Officer
VesPro Scientific Research Group

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A B S T R A C T

Objective

The aim of this study is to assess the clinical efficacy & safety of PRULEVA™ Easy Cream as a safe, easy & effective botanical based immuno-modulatory cream indicated for moderate to severe refractory (resistant to treatment) atopic dermatitis (AD) in adults & pre-school children involving larger affected body surface areas without causing transient or permanent skin thinning, adrenal suppression, post-treatment hyperpigmentation or striae (stretch marks).

Design

- A multicenter, open-label non-randomized pilot study
- 12 weeks for adults. 3 weeks for children.

Subjects

48 volunteer subjects of Asian ethnicity comprising 22 adults (20-45yrs) & 26 pre-school children (3-10 yrs) with relapsing & resistant moderate to severe atopic dermatitis (AD) over a large body area in the face, neck, trunk, arms & extremities.

The 22 adults & 26 pre-school children were divided into 2 categories:

Category A - 11 adults & 13 pre-school children

- These subjects had never administered any topical corticosteroids or topical tacrolimus in the past 2 years.
- They relied only on emollient creams & occlusion.

Category B - 11 adults & 13 pre-school children

- These subjects used topical corticosteroids or topical tacrolimus intermittently only as when necessary (PRN) in the past 2 years.

Each category is divided into 4 groups –
PRULEVA™, Corticosteroid, Tacrolimus & Control. Control Group (n=8) is assigned regular emollients as placebo.

Results

All 3 groups demonstrated similar efficacies in their symptomatic management of acute AD flareups when they are started at the earliest onset of symptoms & used consistently until full control is achieved. The final outcome for each participant are dependent on their comprehension, confidence, consistency & compliance.

The findings of this pilot study revealed an interesting & significant difference in the final outcome in the PRULEVA Group. Participants in the PRULEVA Group demonstrated the highest in safety, compliance confidence & consistency in its repeated usage which has led to more satisfactory outcomes for the participants. Further analysis revealed that only all 16 participants in the PRULEVA Group tested negative for side effects etc no skin thinning, adrenal suppression post treatment hyperpigmentation stretch marks, abnormal skin texture or loss of skin hydrating & moisturising function.

Introduction:

The skin which comprises the epidermis & dermis is a tough physical barrier for preventing pathogenic entry, chemical infiltrations & loss of body fluids. To prevemt infiltration of pathogens, the epidermis contains immune cells such as langerhans cells & dendritic cells for rapid neutralisation of pathogens. The skin is the largest, most visible & physically exposed immune organ.

Immune Modulation

A healthy and competent immune cell in the skin will produce a correct & balanced (well modulated) immune response known as inflammation. The intensity, quantity, quality, duration and timing of an inflammation when produced by a wellmodulated & competent immune cell is extremely precise and is not overly responsive or sensitive (etc allergic), wrongly responsive (etc autoimmune) or non responsive (etc weak immune). It's response is well modulated. Healthy skin with well modulated immune cells does not exhibit any chronic long term redness, persistent rashes, dry, scaly, cracked skin or discoloured patches.

Atopic eczema or atopic dermatitis (AD) is a long term episodic & highly visible abnormal inflammation of the skin which can develop in both childhood & adulthood. AD's exact etiology is unknown but its pathogenesis is multifactorial and involves a complex immunologic cascade which lead to frequent flare ups of itchy skin conditions up to 2 – 3 episodes a month followed by intermittent remissions / relapses. The perpetually itchy,inflamed & cracked skin, sleep loss, social stigmatising & the continuous need for application of messy & oily emollient creams rapidly overwhelm most AD patients especially young children.

Immune Suppression

Topical corticosteroids and topical tacrolimus are clinically proven immune suppressants for managing AD flareups by inhibiting the inflammatory response of immune cells on the skin. It does not attempt to correct or balance (modulate) an overly responsive immune cell, but aggressively silence it into submission. While this method is impressive in the short term but is counter productive in the long term.

A small initial starting dose of corticosteroids or tacrolimus is usually used in the initial months but will progressively lead to higher dosage and potencies in the long term due to Its aggressive inhibitory action causes immune cells to adapt leading to desensitization of the immune cells., thereby requiring higher doses and higher % potency in the future with increased side effects. Therefore, topical corticosteroids and topical tacrolimus are not designed or indicated for repeated long term intermittent use for relapsing & refractory (resistant to treatment) moderate to severe AD when involving large body surface areas especially in children.

Pruleva™

PRULEVA™ is represented as a topical cream consisting of botanicals which are known for their gentle & safe immune modulation properties as opposed to aggressive and harsh immune suppressing properties of synthetic corticosteroids. PRULEVA™'s immune modulating properties assists in developing a correct & balanced immune response during any acute flare ups. PRULEVA™ is indicated for use during intermittent flareups only. Therapy is discontinued when full control of AD flareup is achieved which denotes that the immune response is successfully modulated (balanced) but the positive outcome might not be sustainable as the skin's localised immunity health is continuously influenced and impacted by systemic immunity health.

No topical skin product regardless of it being immune modulatory or immune suppressing can produce sustainable AD remissions. Topical creams are used only to manage acute flare ups. Achieving a sustainable remission in AD is only possible by addressing the systemic immunity. IMMOGEN™ is a botanical beverage indicated for the safe & gentle modulation of systemic immunity.

Momethasone Furoate Cream 0.1%

Momethasone Furoate 0.1% is a US (Class 3) Upper-Mid Strength corticosteroid topical cream in the Betaemethasone Dipropionate Type Class D1. It has a strong immune suppressing action with documented side effects.

Hydrocortisone Acetate 1%

Hydrocortisone 1% is a US (Class 7) Lowest Strength corticosteroid topical cream in the Hydrocortisone Type Class A. It is OTC & most commonly used by pre-school children.

Tacrolimus 0.1%

A non-steroidal topical cream with a highly pronounced immunosuppressive effect via suppression of Interleukin 2 & T-Cells. Originally intended for lowering risk of organ rejection from allogeneic transplant. It also has documented side effects including cancer development and other difficult to treat side effects such as post inflammatory hyperpigmentation.

Participants & Methods

Design

- A multicenter, open-label non-randomized pilot study.
- 12 weeks for adults & 3 weeks for children.

Pruleva™ Group (n=16)

- 6 adults & 10 pre-school children administered PRULEVA™ 3 - 4 times daily. Once full control is achieved, PRULEVA™ is administered 3 times daily on alternate days for 1 week then therapy is discontinued.

Momethasone Furoate 0.1% Group (n=6)

- 6 adults administered Mometasone Furoate Cream 0.1% twice daily as advised by their physicians.
- Once full control is achieved, therapy is discontinued.

Hydrocortisone 1% Group (n=6)

- 6 pre-school children administered Hydrocortisone Cream 1% twice daily as advised by their physicians.
- Once full control is achieved, therapy is discontinued.

Tacrolimus Group (n=12)

- 6 adults & 6 preschool children administered Tacrolimus Ointment 0.1% twice daily as advised by their physicians.
- Once full control is achieved, therapy is discontinued.

Control Group (n=8)

Diagnostics Criterias for Atopic Dermatitis (AD)

By The American Academy of Dermatology Consensus Group (AADCG)

For standardisation of AD diagnostic criterias, this pilot study requires all dermatologists to employ The American Academy Of Dermatology Consensus Group Group (AADCG) recommended diagnostic criteria for AD as it is the most streamlined, practical and reliable diagnostic criteria for AD not requiring laboratory testing.

1. Essential Features

Must be present in all AD patients :

- Pruritus (Itching) with a relapsing history
- Eczema with a relapsing history

2. Important Features

Seen in most AD cases, further adding support to the diagnosis of AD:

- Early age of onset
- Personal and / or family history
- Immunoglobulin E (IgE) reactivity
- Xerosis (Dryness)

3. Associated Features

These clinical associations below may help to suggest the diagnosis of AD but cannot be used singularly for defining or detecting AD:

- Keratosis pilaris
- Pityriasis alba
- Ichthyosis
- Ocular or periorbital changes
- Perifollicular accentuation
- Lichenification
- Prurigo lesions

Scoring Index - SCORAD For Atopic Dermatitis (AD)

is a clinical tool used to assess the extent and severity of eczema (**SCOR**ing **A**topic **D**ermatitis) based on

A: Body Surface Area Scoring

- Head & neck 9%
- Upper limbs 9% each
- Lower limbs 18% each
- Anterior trunk 18%
- Back 18%
- Genitals 1%

B: Intensity Scoring

Absent 0 / Mild 1 / Moderate 2 / Serious 3

- Oozing - Crusting 0-3
- Dryness - Ichthyosis 0-3
- Erythema - Redness 0-3
- Papulation - Swelling 0-3
- Excoriation - Scratching 0-3
- Lichenification - Thickening 0-3

C: Subjective Symptoms Scoring

- Sleep Loss 0-10
- Pruritus (Itch) 0-10

Total Score = A/5 + 7B/2 + C

D: Severity Scoring

- Mild Eczema < 25
- Moderate Eczema 25 – 50
- Severe Eczema > 50

Tertiary Adrenal Suppression (TAS)

Prolonged exogenous (external) supply of synthetic corticosteroid from topicals were clinically proven to cause a partial or total suppression of the adrenal gland's own endogenous (internal) production of natural corticosteroids. Misuse or abuse of topical corticosteroids can cause transient or long term tertiary adrenal suppression (TAS).

Abraham G, Gottschalk J, Ungemach FR. Evidence for topical glucocorticoid-induced decrease in hypothalamic-pituitary-adrenal axis response and liver function. Endocrinology. 2005;146:3163–71. The severity & duration of tertiary adrenal suppression can range from a transient to permanent depending on:

- Amount of topical corticosteroid applied
- Potency % of topical corticosteroid
- Size of body surface area to be applied
- Existing skin thickness
- Duration of treatment
- How frequently it is applied
- Location to be applied - Eyelid & scrotum highest absorption
- Cracked or broken skin
- Age of the patient - Children have increased absorption
- Type of format - Ointments increase penetration

Symptoms

Chronic Fatigue, Anxiety, Insomnia, Weight Gain, Low ACTH, Low Cortisol etc.

Diagnostic Criteria

Adrenal insufficiency are generally diagnosed by the standard-dose ACTH test, which is safe, reliable and accurate for paediatrics & adults.

Gleeson HK, Walker BR, Seckl JR, Padfi eld PL. Ten years on: safety of ACTH tests in assessing adrenocorticotropin deficiency in clinical practice. J Clin Endocrinol Metab 2003;

Low Dose Corticotropin Test (1 ug or 500 ng)

Normal : Peak cortisol > 500 nmol/L
Adrenal Insufficiency : Peak cortisol < 500 nmol/L
Same parameters apply for paediatrics & adult

Severity Grading of Adrenal Insufficiency

Grade 1 : Asymptomatic
Grade 2 : Symptomatic
Grade 3 : Hospitalisation

Dermal Atrophy (DA)

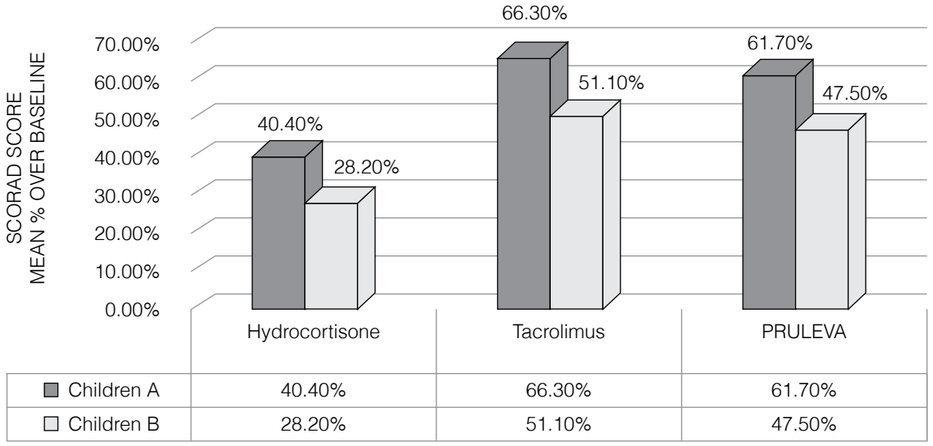
Chronic use of topical corticosteroids or tacrolimus can lead to undesirable skin thinning (atrophy), stretch marks (striae), hypo & hyper pigmentation.

High Resolution Measurement of Dermal Atrophy

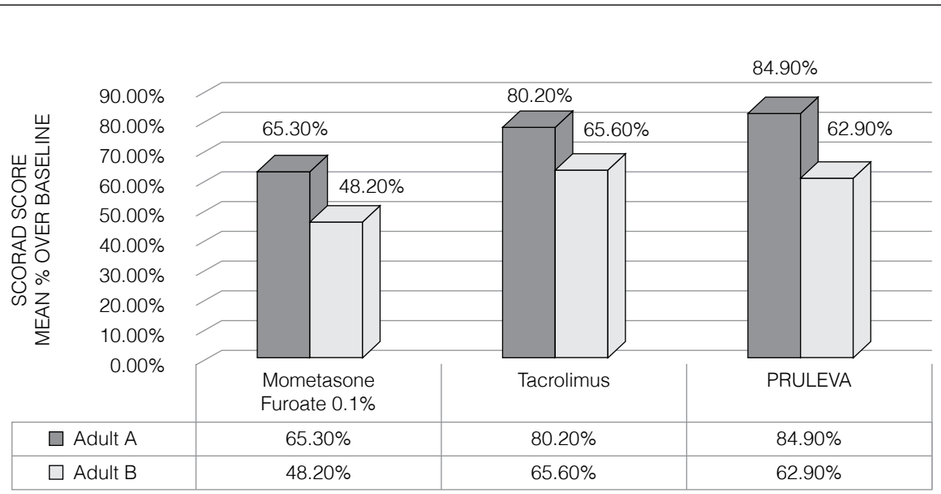
Conducted by 22Mhz UltraScan UC 22 UltraSound
by CK Electronics Gmbh Germany. 72 µm resolution

CHILDREN Category A **N=11** **Efficacy at Week 3**			
	N=5	N=3	N=3
	Hydrocortisone 1% Twice Daily	Tacrolimus 0.03% Twice Daily	PRULEVA 3-4 Times Daily
SCORAD Score			
Median % Improvement Over Baseline	40.4 %	66.3 %	61.7 %
Dermal Atrophy			
Median % Skin Atrophy Over Baseline	4.0 %	0.0 %	0.0 %
Adrenal Suppression			
Grade 1 (Asymptomatic) Grade 2 (Symptomatic)	Nil Nil	Nil Nil	Nil Nil
Post Inflammatory Pigmentation	Nil	Nil	Nil

CHILDREN Category B **N=11** **Efficacy at Week 3**			
	N=5	N=3	N=3
	Hydrocortisone 1% Twice Daily	Tacrolimus 0.03% Twice Daily	PRULEVA 3-4 Times Daily
SCORAD Score			
Median % Improvement Over Baseline	28.2 %	51.1 %	47.5 %
Dermal Atrophy			
Median % Skin Atrophy Over Baseline	6.0 %	0.0 %	0.0 %
Adrenal Suppression			
Grade 1 (Asymptomatic) Grade 2 (Symptomatic)	N=3 (27%) Nil	Nil Nil	Nil Nil
Post Inflammatory Pigmentation	N=3	Nil	Nil



Children A	40.40%	66.30%	61.70%
Children B	28.20%	51.10%	47.50%



Adult A	65.30%	80.20%	84.90%
Adult B	48.20%	65.60%	62.90%

ADULT Category A (N=9) Efficacy at Week 12			
	N=3	N=3	N=3
	Mometasone 1% Furoate Twice Daily	Tacrolimus 0.1% Twice Daily	PRULEVA 3-4 Times Daily
SCORAD Score			
Median % Improvement Relative To Baseline	65.3 %	80.2%	84.9
Dermal Atrophy			
Median % Skin Atrophy Relative To Baseline	15%	Nil	Nil
Adrenal Suppression			
Grade 1 (Asymptomatic) Grade 2 (Symptomatic)	N = 2 (22%) Nil	Nil Nil	Nil Nil
Post Inflammatory Pigmentation	Nil	Nil	Nil

ADULT Category B (N=9) Efficacy at Week 12			
	N=3	N=3	N=3
	Mometasone 1% Furoate Twice Daily	Tacrolimus 0.1% Twice Daily	PRULEVA 3-4 Times Daily
SCORAD Score			
Median % Improvement Relative To Baseline	48.2 %	65.6	62.9
Dermal Atrophy			
Median % Skin Atrophy Relative To Baseline	18%	Nil	Nil
Adrenal Suppression			
Grade 1 (Asymptomatic) Grade 2 (Symptomatic)	N = 2 (22%) N = 1 (11%)	Nil Nil	Nil Nil
Post Inflammatory Pigmentation	N =1 (11%)	N=1 (11%)	Nil

Conclusion

For Category A (adults & children)

The adults & children have not administered any topical corticosteroids in the past 2 years and relied solely on emollients & occlusion in the management of their AD therefore have no prior desensitization, attenuation or compromised integrity in their skin's immune cells. As such, Category A exhibited the highest & most impressive outcomes / improvements in the SCORAD for hydrocortisone, tacrolimus & PRULEVA irrespective of age.

Both PRULEVA & Tacrolimus have similar scores which are significantly higher than Hydrocortisone based on reasons provided by participants below deliberately reducing quantity & frequency of application of corticosteroids due to fear of developing difficult to treat hypopigmentation & adrenal suppression.

For Category B (adults & children)

The adults & children administered topical steroids frequently on an intermittent "as when necessary" PRN basis and therefore have accumulated certain degree of desensitization and attenuation in their skin's immune cells which has significantly reduced the effectiveness / response of hydrocortisone, tacrolimus and Pruleva. As such, it can be hypothesized that immune cells which are desensitized are significantly less responsive to further immune suppression from hydrocortisone, tacrolimus or immune modulation.

It is also clinically proven that previous prolonged use, misuse or abuse of corticosteroids of any type, can damage immune cells and melanocytes resulting in an risks of post inflammatory hyper or hypopigmentation.

The exact mechanism of how corticosteroid temporarily or permanently disrupts the function of melanocytes, collagen and elastin production is still unclear. However, it is clear that topical corticosteroids use, misuse or prolonged usage can result in transient or permanent collagen / elastin degradation, melanocyte abnormality, dysregulation in hydration and other hosts of difficult & expensive to treat steroidal side effects.

A small & insignificant advantage in the rapid onset of action in corticosteroids as an "instant gratification" topical drug of choice for managing AD flare ups is heavily outweighed by its expensive & difficult to treat local and systemic side effects as well the complex damage and dysregulation it inflicts on otherwise healthy immune skin cells and melanocytes.

Presentation by:

Nutrawell Marketing
C/O Antah Pharma Sdn. Bhd.
No. 3, Jalan 19/1, 46300 Petaling Jaya,
Selangor Darul Ehsan, Malaysia.
Tel: 03 7956 7677
Web: www.nutrawell.com.my.