Immogen™

A PILOT INTERVENTION STUDY

Immogen™ Immuno-Modulatory Nutrition for Long Term Treatment of Moderate to Severe Refractory Atopic Dermatitis (AD) in Adults

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IMMOGEN™ is an immune modulatory nutrition custom manufactured by VesPro Life Sciences in Olathe, Kansas US for Nutrawell Marketing Sdn. Bhd.

IMMUNO-MODULATORY NUTRITION FOR LONG TERM TREATMENT OF MODERATE TO SEVERE REFRACTORY ATOPIC DERMATITIS (AD) IN ADULTS

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Abstract

Objective
The aim of this study is to assess the efficacy & safety of IMMOGEN™ immuno-modulatory nutrition as a more practical long term treatment for refractory (resistant to treatment) moderate to severe AD in adults involving larger affected body surface areas without risk of immune suppression

Subjects
24 volunteer adult patients with resistant/relapsing moderate to severe atopic dermatitis (AD) were assigned into 4 groups over a period of 40 days.
No placebo or randomisation was initiated.

Control Group (n6)
Lifestyle & Dietary Intervention Only

Strict avoidance of
– Immune stimulatory type dietary supplements, herbs & spices
– Dietary allergens etc gluten, soy sauce, milk, wheat & cereals
– Direct sunlight & heat
– Mental stress

Strict compliance for
– Early sleep
– Relaxation techniques
– Identification & avoidance of all known trigger factors. No emollient

Immune Suppressive Group (n6)

Day 1 – 3 (Flare ups)	Topical 0.1% Tacrolimus Or Topical 0.05% Betamethasone Dipropionate Applied twice a day until remission is achieved 0.5mg Xanax XR 1 tablet/day for anxiety & sleep No lifestyle or dietary changes. No emollients
Day 4 – 40 (Prophylaxis)	Topical 0.1% Tacrolimus or Or Topical 0.05% Betamethasone Dipropionate Applied once every 3 days 0.5mg Xanax XR 1 tablet/day for anxiety & sleep No lifestyle or dietary changes. No emollients

Immune Modulation Group (n6)

Day 1 – 3 (Flare ups)	IMMOGEN™ 10 grams	3 times per day
Day 4 – 14 (Therapy)	IMMOGEN™ 5 grams	3 times per day
Day 15 – 40 (Prophylaxis)	IMMOGEN™ 5 grams	Once daily
Topical Emollient		3 times per day

No tacrolimus/corticosteroids creams, lifestyle/dietary changes or anxiolytics

Combination Group (n6)

Day 1 – 3 (Flare ups)	Topical 0.1% Tacrolimus or Betamethasone	
Day 4 – 14 (Therapy)	IMMOGEN™ 5 grams	3 times per day
Day 15 – 40 (Prophylaxis)	IMMOGEN™ 5 grams	Once daily
Topical Emollient		3 times per day

0.5mg Xanax XR 1 tablet everyday for anxiety/sleep
No lifestyle/dietary changes.

Introduction

Atopic eczema or atopic dermatitis (AD) is a long term episodic & highly visible inflammatory skin condition which can develop in both childhood & adulthood. AD's exact etiology is unknown but its pathogenesis is multifactorial and involves a complex immunologic cascade including genetic predisposition, defects in immune response, dietary allergens and disruption of the epidermal barrier all of 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.

While topical corticosteroids or topical tacrolimus provide rapid and immediate onset of action and effective short term control of acute flare-ups, they are not designed or indicated for repeated long term use for relapsing & refractory (resistant to treatment) moderate to severe AD involving large body surface areas.

This is due to both topical steroid and tacrolimus's tachyphylaxis characteristic where a small initial starting dose in the initial months will progressively lead to higher dosage and potencies in the long term due to desensitization of the Langerhans immune cells in the stratum spinosum of the epidermis. When administered over larger body surface areas and in higher potencies in the long term, these topical agents will eventually infiltrate into internal systemic circulation via large areas of cracked, inflamed & vasodilated skin to exert an adverse effect on the patient's systemic immunity and hepatic function. Additionally, the risk of a rebound/flareup phenomenon upon cessation of use, elevated liver enzymes and irreversible skin atrophy risks are all justifiable key clinical concerns which have resulted in patient's reluctance, distrust and poor compliance for topical steroids in the long term.

This pilot study has clinically proven, validated and justified the patients' long term safety concerns and reluctance with immune status screening results & hepatic enzyme profile testing.

The primary objective of this study is to determine the effectiveness and safety of an immune modulatory nutrition IMMOGEN™ to reduce the frequency and severity of flare-ups in relapsing & refractory "resistant to treatment" AD involving large body surface areas. The reduced flareups and severity from the use of IMMOGEN™ will greatly reduce repeated exposure to topical steroids & tacrolimus.

Participants & Methods

Design

A 40 day pilot, multicenter, open-label, non randomized study

Selection of Subjects

24 adult subjects (19 females & 5 males) in the age group of 30 – 49 who volunteered for this pilot study were positively diagnosed with atopic dermatitis (AD) by their dermatologist in their respective home states.

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 (AADCG) recommended diagnostic criteria for AD as it is the most streamlined, practical and reliable diagnosing criteria for AD not requiring laboratory testing.

1: ESSENTIAL FEATURES

Must be present in all AD patients :

- Pruritus (Itchy skin condition) with a relapsing history
- Eczema (Acute or Chronic) 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 :

- Atypical vascular responses
- (facial pallor & delayed blanch response)
- Keratosis pilaris
- Pityriasis alba
- Hyperlinear palms
- Ichthyosis
- Ocular or periorbital changes
- Other regional findings
- (eg, perioral changes/periauricular lesions)
- Perifollicular accentuation
- Lichenification
- Prurigo lesions

4: EXCLUSIONARY CONDITIONS

These conditions below must be excluded :

- Contact dermatitis (irritant or allergic)
- Seborrheic dermatitis
- Psoriasis
- Scabies Ichthyoses
- Cutaneous T-cell lymphoma
- Photosensitivity dermatoses

ATOPIC DERMATITIS (AD) SCORING INDEX

SCORAD is a clinical tool used to assess the extent and severity of eczema (SCORing Atopic Dermatitis) 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

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

C: Subjective Symptoms Scoring

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

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

Severity Scoring

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

ASSESSMENT MARKERS FOR IMMUNE FUNCTION

The severely impaired epidermal barrier function in relapsing AD patients facilitates more rapid cutaneous penetration of any topical immune suppressive agents into systemic vessel independently from its potency. Additionally, the vasodilation prevalent in most eczema affected body surface area caused by PGE2 (Prostaglandin 2) elevations can cause more rapid uptake of topical agents into systemic circulation.

Therefore, the risk of systemic side effects associated with frequent and repeated long term use of topical immune suppressive agents increases with higher-potency topical formulations.

The most representative laboratory marker for assessing immune status is CD4 cell count expressed in cells per cubic millimetre.

CD4 cells is a form of lymphocyte that fights infection. It is made in the spleen, lymph nodes and thymus gland and is the most important component of our humoral immunity.

Clinical Reference Range
CD4 500-1500 cells / µL

As CD4 cell count degrades below 200 cells / µL, there is an increased risk of opportunistic infections (OI). This pilot study attempts to assess the immunity status for each study group during the 40 day trial.

ASSESSMENT MARKERS FOR HEPATIC FUNCTION

Long term repeated administration of topical corticosteroids or tacrolimus requires clinical vigilance in the close monitoring of hepatic enzyme elevations.

Clinical Reference Range
SGOT (AST) 5 – 40 µ/L
SGPT (ALT) 7 – 56 µ/L
GGT 0 – 45 µ/L

TIME POINT OF ASSESSMENT

T0 – Baseline Established
T1 – 3 days after entry
T2 – 7 days after entry
T3 – 15 days after entry with hepatic/immune assessment
T4 – 20 days after entry
T5 – 30 days after entry with hepatic/immune assessment
T6 – 40 days after entry

APPENDIX A

Assessment Marker For Hepatic Function	Baseline			T3 (15 days after entry)			T5 (30 days after entry)		
	AST	ALT	GGT	AST	ALT	GGT	AST	ALT	GGT
	5 – 40 µ/L	7 – 56 µ/L	0 – 45 µ/L	5 – 40 µ/L	7 – 56 µ/L	0 – 45 µ/L	5 – 40 µ/L	7 – 56 µ/L	0 – 45 µ/L
Control Group	15.80 ± 1.45	9.06 ± 2.77	5.88 ± 1.90	15.00 ± 1.09	8.12 ± 2.02	4.90 ± 2.56	12.90 ± 1.80	9.12 ± 2.77	4.43 ± 2.66
Immune Suppressive Group	14.20 ± 2.00	10.12 ± 1.68	6.26 ± 1.39	27.13 ± 1.90	29.20 ± 1.33	18.50 ± 3.55	32.34 ± 3.45	47.06 ± 2.90	30.34 ± 3.55
Immune Modulation Group	11.00 ± 3.88	9.86 ± 2.90	6.12 ± 3.62	11.75 ± 3.89	8.39 ± 2.86	5.80 ± 2.37	10.32 ± 2.12	5.90 ± 1.33	5.10 ± 1.90
Combination Group	13.12 ± 2.13	12.58 ± 2.43	5.87 ± 2.15	11.70 ± 1.12	10.20 ± 3.13	5.10 ± 1.66	11.00 ± 1.90	10.45 ± 2.55	5.70 ± 2.87

All groups showed normal hepatic function except for the immune suppressive group. Significant elevation in liver enzymes were detected at T3 for the Immune Suppresive Group.

APPENDIX B

Assessment Marker For Immune Functions	Baseline	T3 (15 days after entry)	T5 (30 days after entry)
	CD4 500 – 1500 cells/µL	CD4 500 – 1500 cells/µL	CD4 500 – 1500 cells/µL
Control Group	1100 ± 150	1027 ± 225	1105 ± 109
Immune Suppressive Group	983 ± 116	861 ± 89	714 ± 73
Immune Modulation Group	930 ± 85	987 ± 120	1067 ± 149
Combination Group	1020 ± 45	1157 ± 77	1181 ± 61

All groups demonstrated normal immune function except for the immune suppressive group. Significant decline in CD4 lymphocytes were detected at T3 for the Immune Suppressive Group The safety findings above provides clinical evidence that 0.05% topical corticosteroids and 0.1% tacrolimus administered over larger body surface areas will eventually infiltrate into internal systemic circulation via large areas of cracked, inflamed & vasodilated skin to exert an adverse effect on hepatic function & systemic immunity.

APPENDIX C

	Time Point of Assessment						
	T0	T1	T2	T3	T4	T5	T6
	Baseline	3 days after entry	7 days after entry	15 days after entry	20 days after entry	30 days after entry	40 days after entry

	Score	Score	% Var. T1-T0	Score	% Var. T2-T0	Score	% Var. T3-T0	Score	% Var. T4-T0	Score	% Var. T5-T0	Score	% Var. T6-T0
Control Group (n6) SCORAD Eczema Severity Scoring													
A: Body Surface Area Scoring	110	110	0.0	110	0.0	110	0.0	110	0.0	130	18.2	130	18.2
B: Intensity Scoring	65	65	0.0	65	0.0	61	– 6.2	40	– 38.5	60	– 7.7	63	– 3.1
C: Itch & Dryness Scoring	77	77	0.0	77	0.0	60	– 22.1	52	– 32.5	70	– 9.1	74	– 3.9
TOTAL SCORAD Score < 25 Mild Eczema, 25-50 Moderate Eczema, 50 > Severe Eczema	41	41	0.0	41	0.0	37	– 9.8	27	– 34.1	38	– 7.3	40	– 2.4

	Score	Score	% Var. T1-T0	Score	% Var. T2-T0	Score	% Var. T3-T0	Score	% Var. T4-T0	Score	% Var. T5-T0	Score	% Var. T6-T0
Immune Suppressive Group (n6) SCORAD Eczema Severity Scoring													
A: Body Surface Area Scoring	92	92	0.0	92	0.0	92	0.0	92	0.0	134	45.7	134	45.7
B: Intensity Scoring	76	49	– 35.5	47	– 38.2	47	– 38.2	47	– 38.2	58	– 23.7	68	– 10.5
C: Itch & Dryness Scoring	88	45	– 48.9	36	– 59.1	33	– 62.5	33	– 62.5	49	– 44.3	60	– 31.8
TOTAL SCORAD Score < 25 Mild Eczema, 25-50 Moderate Eczema, 50 > Severe Eczema	47	29	– 38.3	27	– 42.6	27	– 42.6	27	– 42.6	35	– 25.5	41	– 12.8

	Score	Score	% Var. T1-T0	Score	% Var. T2-T0	Score	% Var. T3-T0	Score	% Var. T4-T0	Score	% Var. T5-T0	Score	% Var. T6-T0
Immune Modulation Group (n6) SCORAD Eczema Severity Scoring													
A: Body Surface Area Scoring	113	113	0.0	113	0.0	113	0.0	113	0.0	88	– 22.1	85	– 24.8
B: Intensity Scoring	78	55	– 29.5	42	– 46.2	36	– 53.9	31	– 60.3	30	– 61.5	28	– 64.1
C: Itch & Dryness Scoring	95	65	– 31.6	59	– 37.9	57	– 40.0	56	– 41.1	35	– 63.2	34	– 64.2
TOTAL SCORAD Score < 25 Mild Eczema, 25-50 Moderate Eczema, 50 > Severe Eczema	49	35	– 28.5	29	– 40.8	26	– 46.9	23	– 53.1	20	– 59.2	19	– 61.2

	Score	Score	% Var. T1-T0	Score	% Var. T2-T0	Score	% Var. T3-T0	Score	% Var. T4-T0	Score	% Var. T5-T0	Score	% Var. T6-T0
Combination Group (n6) SCORAD Eczema Severity Scoring													
A: Body Surface Area Scoring	125	125	0.0	125	0.0	125	0.0	125	0.0	118	– 5.6	105	– 16.0
B: Intensity Scoring	95	58	– 38.9	43	– 54.7	40	– 57 9	38	– 60.0	32	– 66.3	32	– 66.3
C: Itch & Dryness Scoring	90	51	– 43.3	48	– 46.7	39	– 56.7	39	– 56.7	34	– 62.2	32	– 64.4
TOTAL SCORAD Score < 25 Mild Eczema, 25-50 Moderate Eczema, 50 > Severe Eczema	56	35	– 37.5	28	– 50.0	26	– 53.6	25	– 55.4	21	– 62.5	21	– 62.5

RESULTS

Control Group

All 6 subjects in the control group are highly conservative individuals with moderate eczema who refuse topical or oral allopathic treatments for treating their AD flareups, prefering a strict avoidance diet to control their flare-ups and manage their existing conditions. With the avoidance diet, their flare ups & itch showed only marginal remission after 10 days.

Consequently all 6 subjects are of the opinion that avoidance diet are not effective in controlling acute AD flare-ups and a more specialised intervention was necessary for such acute conditions. They managed to be compliant on the avoidance diet for the initial 20 days but reverted to their regular diet thereafter citing dieting fatigue, heightened sense of deprivation, uncontrollable cravings, family & social pressure.

The subjects concluded that avoidance diet for AD though clinically proven and validated but is socially unrealistic, impractical and stressful. 10 days after cessation of the avoidance diet, rebound phenomenon such as flare-ups and digestive discomforts occurred during the abrupt re-introduction of their regular daily diet. 2 of 6 subjects also developed flare-ups in new body surface areas (upper limbs) as no systemic treatment was administered to the immune system

Immune Suppression Group

It is clinically observed and validated that the most significant modality for rapid onset of action and efficacy in management of AD flare-ups and itch within 3 days is a twice daily application of topical corticosteroids or tacrolimus. Thereafter, topical corticosteroid or tacrolimus applied once every 3 days were sufficient in preventing episodic relapses.

Despite this, all 6 subjects discontinue use of all topicals in the 3rd week due to patients' concern of hepatic and immune dysregulation based on blood safety assay results. In the 4th week upon cessation of topical corticosteroids and tacrolimus, rebound flare-ups were observed in 1 of 6 subjects also developed flares in new body surface areas (face and neck)

Immune Modulation Group

This group demonstrated a gradual and the most sustainable reduction in body surface area scoring, intensity scoring and itch scoring compared to the immune suppression group and control group due to the systemic immune modulatory and tissue regenerating effects of both the IMMOGEN™ Nutrition.

This group displayed a longer onset of action for itch control (7 days) compared to only 3 days for the immune suppressive group using exclusively corticosteroids.

At the moment of this writing, corticosteroids provides the most rapid onset of action for itch scoring.

Combination Group

The combination group uses corticosteroid cream for Day 0-3 only to provide the most rapid relief for intensity, itch & dryness followed by Day 4 - 40 with both immune modulatory IMMOGEN™ nutrition and immune modulatory emollient cream The objective was to combine the best of all modalities of AD treatment for the most ideal outcome.

However 4 of 6 patients in this group were not compliant in the switchover timing for the topicals. Patients' justification for non compliance was due to the group having the most severe eczema conditions with the highest eczema baseline score of 56 compared to the other study groups.This group's eczema conditions are the most delinquent, resistant and recurrent thereby requiring extended use of steroid creams until Day 15.

From Day 16 – 40, they switched to the regenerative immune modulatory cream. Immune modulatory cream cannot be used concomitantly with immune suppressive steroid creams.

This late switchover from the steroid cream with its catabolic (tissue breakdown) characteristics to the tissue regenerative immune modulating cream represented a significant delay in the healing of affected body surface areas in the combination group.

As a result of this non compliance, the improvement to body surface scoring is only 16% (T4) as test subjects administered the tissue regenerative immune modulatory cream for only 24 days (Day 16 to Day 40)

Comparatively, the immune modulatory group scored an impressive improvement of 24.8% (T4) in body surface area scoring as its subjects administered the tissue regenerative cream and IMMOGEN™ nutrition for a continuous 40 days (Day 1 to Day 40)

It can be hypothesized that longer duration of IMMOGEN™ nutrition and tissue regenerative cream use will result in significant healing and normalising of skin cells and consequently produce a better improvement in body surface area improvement scoring and total SCORAD score.

CONCLUSION

Our scientific panel hypothesized that in the absence of any contingencies or non compliance,in all groups, the overall improvements % in the total SCORAD score and clinical outcomes of the combination group & immune modulatory group are the highest and similar. Both groups have similar safety marker profiles

The only clinical difference is that the patients' itch control is achieved much sooner in 3 days in the combination group compared to 7 days for the immune modulatory group (as advised by test subjects in both groups) and that patients are aware that steroid creams are catabolic which results in slow tissue healing while immune modulatory nutrition and creams provides an additional cell regenerative function. All corticosteroids creams have a catabolic (tissue breakdown) effect that prevents, disrupts or retards regeneration of the epidermis. 6 patients in this study noticed formation of abnormal longitudinal shaped scars from repeated use of catabolic steroids.

The texture of steroid creams, tacrolimus and immune modulatory cream are slightly coarse, gritty & tacky. Immune modulatory cream is reported by test subjects as having the lightest & smoothest texture when shaken well immediately before each use.

Patients are demanding for topicals which possesses tissue regenerating qualities for rebuilding eczema damaged skin cells, itch control, intensity control, hydration and possesses an immune normalising characteristic (modulatory) compared to catabolic & immune inhibitory steroids creams.

Immune modulatory normalising creams cannot be used concomitantly with immune suppressive steroid creams.

Comments

The result of this pilot intervention study supports the recommendation that IMMOGEN™ Immune-Modulatory Nutrition is physician recommended & patient approved for the safe and effective long term treatment of refractory "resistant to treatment" AD in adults involving large body surface areas without risks of immune suppression or dysregulation.

Author
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