EFFICACY AND SAFETY OF CALCIPOTRIOL OINTMENT VS DESOXIMETASONE OINTMENT IN THE TREATMENT OF CHRONIC HAND ECZEMA: A DOUBLE-BLINDED, RANDOMIZED RIGHT-LEFT COMPARISON TRIAL

BY

MISS RATCHASIN PONGPRASERT

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER DEGREE OF SCIENCE (DERMATOLOGY)
CHULABHORN INTERNATIONAL COLLEGE OF MEDICINE
THAMMASAT UNIVERSITY
ACADEMIC YEAR 2016

EFFICACY AND SAFETY OF CALCIPOTRIOL OINTMENT VS DESOXIMETASONE OINTMENT IN THE TREATMENT OF CHRONIC HAND ECZEMA: A DOUBLE-BLINDED, RANDOMIZED RIGHT-LEFT COMPARISON TRIAL

BY

MISS RATCHASIN PONGPRASERT

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER DEGREE OF SCIENCE (DERMATOLOGY)

CHULABHORN INTERNATIONAL COLLEGE OF MEDICINE

THAMMASAT UNIVERSITY

ACADEMIC YEAR 2016

THAMMASAT UNIVERSITY
CHULABHORN INTERNATIONAL COLLEGE OF MEDICINE

THESIS

BY
MISS RATCHASIN PONGPRASERT

ENTITLED

EFFICACY AND SAFETY OF CALCIPOTRIOL OINTMENT VS DESOXIMETASONE OINTMENT IN THE TREATMENT OF CHRONIC HAND ECZEMA: A DOUBLE-BLINDED, RANDOMIZED RIGHT-LEFT COMPARISON TRIAL

was approved as partial fulfillment of the requirements for
the degree of Master degree
on Approval date May 26, 2017

Chairman _____
(Assistant Professor Ploysyne Rattanakaemakorn, M.D.)

Member and Advisor _____
(Premjit Juntongjin, M.D.)

Member _____
(Assistant Professor Padcha Pongcharoen, M.D.)

Director, Graduate Studies _____
(Professor Kesara Na-Bangchang, Ph.D.)

Dean _____
(Associate Professor Kammal Kumar Pawa, M.D.)

Thesis Title	EFFICACY AND SAFETY OF CALCIPOTRIOL OINTMENT VS DESOXIMETASONE OINTMENT IN THE TREATMENT OF CHRONIC HAND ECZEMA: A DOUBLE-BLINDED, RANDOMIZED RIGHT-LEFT COMPARISON TRIAL
Author	Miss Ratchasin Pongprasert
Degree	Master degree
Major Field/Faculty/University	Science (Dermatology) Chulabhorn international college of medicine Thammasat University
Thesis Advisor	Premjit Juntongjin, M.D.
Academic Years	2016

ABSTRACT

Chronic hand eczema is a common dermatologic condition which frequently relapses and has poor response to conventional therapies. Topical potent corticosteroids is the treatment of choice for chronic hand eczema (CHE). However, it prone to induce considerable side effects after long-term usage. Topical vitamin D analogues has been approved in the treatment of psoriasis and was reported to achieve beneficial effect in many other inflammatory diseases. The aim of this research is to assess the efficacy and safety of calcipotriol ointment comparing to desoximetasone ointment in the treatment of CHE. Patients who reach the inclusion criteria were recruited and both of their hands were randomized either to be treated with calcipotriol or desoximetasone ointment twice daily for 8 weeks. Four weeks after discontinuation of the treatment, recurrence was assessed. The efficacy was evaluated by HECSI scores and patient self's assessment at baseline, the 2^{nd}, 6^{th}, 8^{th} and 12^{th} week and digital photographs were taking at baseline, 8^{th} week and 12^{th} week. Any adverse reaction was

recorded during the experiment. The result revealed a statistically improvement of mean HECSI compared to the baseline sine the 2nd week of treatment ($p < 0.001$) and reached 75% reduction by the end of treatment period with no significant difference between the two regimens ($p > 0.05$). Almost all subjects reported more than 50% improvement at the end of the study. The most common side effect for calcipotriol was mild scaling and mild dryness for desoximetasone. In conclusion calcipotriol is as effective as desoximetasone and safe for chronic hand eczema which may further considered as an alternative treatment.

Keywords: chronic hand eczema, calcipotriol, topical vitamin D analogues, desoximetasone, treatment

ACKNOWLEDGEMENTS

I would like to extend my profound appreciation to every individual who provided generous support and contributed in many way to the work described in my thesis. First, I would like to express my deep and sincere gratitude to my thesis advisor, Dr. Premjit Juntongjin for her expedient support and encouragement. Because of her expertise and guidance, this thesis would be able to be completed.

Moreover, I would like to offer my appreciations to all the professional committee members, Assistant Professor Ploysyne Rattanakaemakorn and Assistant Professor Padcha Pongcharoen for the helpful suggestion and beneficial concept to this thesis.

Finally, I am also grateful to all the vise knowledge and encouragement given from Chulabhorn International College of Medicine and also all the support from those who have assisted me in carrying out this thesis.

Miss Ratchasin Pongprasert

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Symbols/Abbreviations	Terms
CHE	Chronic hand eczema
d	Day(s)
HPA	Hypothalamic-pituitary-adrenal
mg	Milligram(s)
mo	Month(s)
PUVA	Psoralen and ultraviolet A
UVA	Ultraviolet A
UVB	Ultraviolet B
wk	Week(s)

CHAPTER 1
INTRODUCTION

Background and rationale

Chronic hand eczema(CHE) is the term for an inflammatory process which primarily involve the hand and lasts longer than 3 months or recurrents at least twice yearly even with a sufficient management and treatment adherence (1). It is one of the common inflammatory skin disorders that consistently relapse and has a concrete negative impact on health socio-economic of many individuals. The prevalence has been indicated up to 14% in general population (1). Approximately 30% of the patients reported working impairment and productivity loss (2). The pathogenesis of hand eczema is multifactorial etiologies since it has different causes and prognoses thus it makes the management complex (3). The common etiologies are involved exogeneous factors such as irritatation, contact with allergens or any immediate-type allergens and endogenous factors for instance atopic dermatitis and psoriasis (4).

Many therapeutic modalities have been prescribed for the treatment of chronic hand eczema including topical medications (topical application of corticosteroids alone or apply together with other agents such as emollients, calcineurin inhibitors or retinoic acid), systemic treatments such as systemic retinoid or others immunomodulating agents, phototherapy and skin protection program (education and avoidance of irritants and contact allergens) (3). Most of them show satisfactory results; however, prone to induce side effects (4). Topical potent and super potent corticosteroids are considered as the mainstay treatment for CHE; nevertheless, numerous disadvantages, including tachyphylaxis, skin atrophy, and adrenal suppression, from chronic application of topical corticosteroids should be monitored.

Topical vitamin D analogues are synthetic modified side-chain of 1α, 25-dihydroxyvitamin D3. They specifically bind to the vitamin D receptor presenting on keratinocytes, melanocytes and various inflammatory cells. Therefore, it regulates keratinocyte proliferation, influence differentiation and inhibit inflamatory effect (5). The anti-inflammatory effects of topical vitamin D analogue is exhibited by inhibition

of cytotoxic T-cells and NK cells and also downregulation of many inflammatory cytokines (6, 7); therefore, calcipotriol, a synthetic topical vitamin D derivatives, has been approved to use in the treatment of plaque type psoriasis in adult and was reported to achieve beneficial effect in the treatment of other inflammatory dermatoses including morphea, vitiligo and ichthyoses which share several pathogenic characters including impaired differentiation and increase proliferation of keratinocyte (8, 9).

Generally, topical vitamin D analogues is well tolerated; nevertheless, common side effects after a prolong or excessive application are irritation and desquamation. Rarely, hypercalcemia and hyperuricemia might be noticed in those using more than 100 g of calcipotriol per week (10).

Previously, there were two studies reporting the successful treatment of topical vitamin D derivatine alone (11) and in combination with topical corticosteroids (12) in chronic palmoplantar dermatitis. However, a randomized controlled trial of topical vitamin D analogues in the treatment of CHE is lacking. Therefore, this study aims to demonstrate whether topical calcipotriol alone is as effective as standard topical corticosteroids monotherapy in the treatment of CHE.

CHAPTER 2
REVIEW OF LITERATURE

2.1 Hand eczema

2.1.1 Introduction

Chronic hand eczema(CHE) is an inflamatory process that primarily or especially involves the hands which exhibit longer than 3 months or relapses at least two times yearly in spite of a sufficient treatment and treatment adherence (13). It is a common dermatologic condition that repeatedly deteriorate and tend to have a poor response to many conventional treatment (4, 13).

Chronic hand eczema has a considerable socio-medical and significant health economic impact on individual live. It is reported as the most common occupational disease (14) and also the cause of significant morbidity, loss of income and has a serious negative impacts on occupational, domestic, and socio-psychological function of the patients (2).

In a cross-sectional multicenter study conducted in 10 European centers, 28% reported unable to work and 12 % informed sick leave because of hand eczema for longer than 5 weeks (15). Another study is a web-based, cross-sectional survey that conducted in the United States. This study informed that approximately 30 % of participants diagnosed with CHE reported impairment while working and productivity loss (2). Moreover, As stated in the study conducted with 1,163 chronic hand eczema patients recruited by 95 centers in German, up to 70% of chronic hand eczema cases encountered a severe disease while only 9.6% of the participants demonstrate as disease clear or almost clear (16). In addition, the treatment of CHE was also proven to be difficult and complicate for dermatologists to manage (2).

2.1.2 Epidemiology

Hand eczema is a common dermatologic condition found in general population and affects all age groups. Based on studies conducted during 1964 to 2007 reported that hand eczema has the point prevalence around 4%, the estimated one-year prevalence around 10% and approximately 15 % of the lifetime prevalence (17-20).

Contact allergy, atopic dermatitis, female sex, and wet work were reported to be an associated factor with a high incidence rate of chronic hand eczema (19). The most frequently reported occupation among 944 patients in the study conducted in German were industrial worker (32%) followed by nursing and healthcare worker (20.9%), office worker (10.2%), cleaning worker (5.6%), hairdressers and beauticians (5.4%) and animal farming (1.6%) (16).

Hand eczema can exhibit in all age groups but it was frequently reported to begin in an early age. The onset of the disease occurred before the age of 20 years in approximately one-third of hand eczema patients (3) with around 7% occur between 12 to16 years of age and 10% at 16 to19 years of age (21).

The early onset of hand dermatitis thought to be associated with atopy (4). In a cohort study of adolescents and young adults followed-up for approximately 15 years, the estimated incidence of hand eczema is approximately 9 to 12 per 1000 person-years (22).

2.1.3 Etiology and pathogenesis

The pathogenesis of hand eczema is multifactorial etiologies since it has different causes and prognoses thus it makes the management complex. The most reported cause of chronic hand eczema is irritant contact dermatitis, involved 45% of patients participated in the multicenter study, followed by atopic hand eczema which is 34% and 23% with allergic contacted dermatitis (4). However, chronic hand eczema can commonly be divided into exogenous, endogenous and idiopathic.

2.1.3.1 Exogenous hand eczema

Exogenous hand eczema refers to the eczematous process caused by the outside environment including chemical or physical factors, organic or inorganic factors interact with the epidermis. The association between etiology and morphology of hand eczema is not evident. Thus, all cases should be investigated for possible allergy. Recently, exogenous hand eczema can be categorized into allergic, irritant and protein contact dermatitis (3).

(1) Irritant contact dermatitis

Irritant contact dermatitis refers to the inflamatory process that caused by prolong or repeated exposure to primary irritants. It is considered as the most common cause of CHE. The severity is depended on the extent of exposure time and

intensity of responsible agent. Main factors influencing hand eczema can be from irritated substances such as detergents, organic solvents, alkaline substances, wet work such as continuous hand washing, occlusive gloves. Based on the German standard of technical rules for hazardous substance, more than 20 times per day of frequent hand washing, having wet hand for more than 2 hours or wearing tight-fitting gloves longer than 2 hours were determined as wet work that can induce irritant hand dermatitis. The occupations found to be associated with irritant hand eczema are domestic workers, health care providers, workers in the construction, hairdressers, food handlers, engineering and electronic industries (13, 15, 23).

Irritant contact dermatitis is the primary cause in patients who diagnosed occupational skin disease. From a population-based study in 5,285 patients, conducted by Center of Occupational and Environmental Dermatology, German, the highest related occupations incidence rates for irritant hand eczema were found in hairdressers followed by, pastry maker and foodmaker (24).

The lesion in most cases diagnosed irritant contact dermatitis is confined to the area of exposure and unlikely to spread to an unexposed site. To diagnose irritant contact dermatitis, dermatologist need to exclude relevant contact allergy and the diagnosis must base on a history of exposure to an irritant (23).

(2) Allergic contact dermatitis

Allergic contact dermatitis exhibit in response to contact with suspected allergens that are competent in penetrating the skin. It is considered as a T-cell mediated delayed-type reaction.

Contact sensitivity is a dermatologic condition which can be exhibit in every individual especially in women. Most common allergen involved metals, rubber chemicals, glues, preservatives, dyes and plant. A cross – sectional study included 1,236 participants in Sør-Varanger municipality, Norway states that the agents found frequently induce allergic reaction were nickel, thiomersal, colophony, and fragrance mix (20).

Other study conducted in 120 health-care provider with hand dermatitis to demonstrates the prevalence of delayed-type and immediate-type hypersensitivity. The most common positive patch test results were nickle sulfate (22%), Thiomersal (13%), Fragrance mix (11.6%), Thiuram mix (5.0%), Epoxy resin

(4%), Cobalt chloride (4%) and Carba mix (3%). The prevalence of natural rubber latex allergy diagnosed by prick testing was 2.5%, and chlorhexidine allergy was <1% (25).

Allergic contact hand eczema should be speculated when patients have a history of suspected occupational-related source including the eczema develop or exacerbate during work, improve or subside on the day-off or resolve on vacation and relapse again after returning to work. In a cross-sectional study demonstrated occupations at risk for severe occupational contact dermatitis which included 1,000 cases of severe occupational contact dermatitis in Denmark, the most frequent occupations developed severe allergic contact dermatitis in women is hairdressers (16.9%) followed by nurses and nursing assistants (15.6%), cleaners (11%), cooks (8.6%), and dental surgery assistants (5.8%). The most frequent occupations developed severe allergic contact dermatitis in men is cooks (7.9%) followed by mechanics and painters (7.3%), cleaners (6.1%), electricians (4.8%) and hairdressers (2.4%) (26).

The risk factors associated with allergic hand eczema are different between women and men. For instant, ear piercing is considered as a significant risk factor for nickel sensitization in women without any significant association found in men. Contact sensitivity was also found significantly associated with atopic dermatitis (AD) and smoking in women but not in men (4, 20, 23).

The diagnosis of allergic contact dermatitis is based on a positive patch test result and a relevant history (either proven or doubtful) which is a relationship between the reaction and allergen exposure or avoidance. Clinical feature of allergic hand eczema incline to present with dyshidrotic or hyperkeratotic or mixed eczema. The lesion is commonly spread from the area that initially expose to causative allergen to an unexposed site. This clinical characteristic may be helpful in verifying the diagnosis. (4, 13, 23).

(3) Protein contact dermatitis

A distinct type of dermatitis induced by both non-immunologic and immunologic mechanism. It is reported in 1976 by Hjorth and Roed-Petersen who found this particular form of contact dermatitis in Danish food handlers, which they called “protein contact dermatitis” (PCD).

The exact pathogenesis is unclear but may involve a IgE mediated hypersensitivity reaction (type I), cell-mediated delayed hypersensitivity (type 4) reaction, and/or a delayed reaction due to IgE-bearing Langerhans cells.

The clinical manifestations characterized by an initial urticarial phase or vesicular flare-up that may become noticeable minutes after contact to suspected substant, followed by eczematous lesion (27, 28). However, it can be presented with the clinical presentation of chronic or recurrent dermatitis, and make it difficult to differentiate between allergic contact dermatitis and other eczematous dermatoses.

The severity can be vary, from localized-generalized urticarial to anaphylactic shock and possible present with multi-systemic disease as it was reported by Von Krogh and Maibach in 1981 (28).

Most common causative proteins involve latex (health care workers), animal and vegetable proteins (food handlers), and animal hair. These causative proteins can be classically categorized into 4 major groups which are (27).

1. Fruits, vegetables, spices, plants, and woods
2. Animal proteins
3. Grains
4. Enzymes

The history of proteins exposure and a positive prick test, or positive result for specific IgE to suspected items are the important aspect for the diagnosis of protein contact eczema. However, Open tests and patch tests are generally negative (15).

2.1.3.2 Endogenous hand eczema

Endogenous hand eczema arises in patient with predisposing factor as an excessive reaction to exogenous trigger or auto-antigens. It is a consequence of an impaired epidermal barrier, and possibly affected by emotional factors (3). There is no exacted external stimuli for endogenous hand eczema. However, it is usually thought to be influenced by genetic factor (3).

(1) Atopic dermatitis

Atopic dermatitis is the condition involved in atopic disease which recently involve 20% of the population in developed countries. It is a major

valuation factor for the development of CHE and also a predisposed factor to persistence and poor prognosis for chronic hand eczema (13, 29).

One third to one half of patients with chronic hand eczema can be considered atopic dermatitis. In a delineation of patients participating European patch testing centers, 5.8% are atopic hand eczema alone and 7.9% are atopic hand eczema with irritant contact hand eczema patients (4, 13, 29).

It is suspected that the irritant contact dermatitis may possibly be the consequent from an epidermal barrier defect in atopic dermatitis. There is an association between the susceptibility to hand eczema and filaggrin gene (FLG) loss of function mutations which is known to be a activated determinant for atopic dermatitis. Filaggrin is a structural protein that play an essential role in the formation of the epidermal barrier and stratum corneum hydration. Loss of filaggrin functional polymorphisms predispose to xerosis, ichthyosis vulgaris, and atopic eczema (30).

A case-control study involved 296 participants report that 12.5% of cases with chronic irritant contact dermatitis found FLG null alleles which is more constantly found when compared with the control group (6.9%). The common type of eczema found among the patients carried these specific alleles were flexural dermatitis with a considerably more lifetime prevalence and atopy score compared than non-carriers (31). Allergic contact eczema tends to develop in a lower number of patients with a history or currently present of atopic disease than in non-atopic. There was almost identical number of positive patch-test result when compared the outcome of atopic with non-atopic patients. However, the reactions of patch-test to constitutive of topical medicaments may be more frequent among atopic patients (3).

Patients with atopic dermatitis can present with vary clinical type, dorsal dry type with fissures, recurrent vesicular or dry volar pattern. The study by Johansen et al. conducted with 710 hand eczema patients to evaluate the correlation between clinical variant of hand dermatitis and etiological diagnosis found no statistically significant corrlation between the clinical types of atopic eczema and etiological diagnosis. Clinical presentation of atopic dermatitis may be relied on genetic factors and the combination between barrier impairment and the inflammatory reaction (32).

(2) Pompholyx

Pompholyx refer to the endogenous form of hand eczema with no relevant contact allergy or any evidence of expose to likely irritant which can induce dermatitis. It is different from the term “Vesicular hand eczema” by this term can be used widely for the eczematous eruption that cause by chronic allergy or irritant contact and also by endogenous vesicular dermatitis.

Clinical manifestation characterized by desolated vesicles that specifically occur on the palms of the hands, especially affect the lateral of the fingers with may or may not be accompanied by variable level of erythema and excessive pruritus. It may last 2-3 weeks and clears with desquamation or completely resolution. The relapse can be stimulated by stress, others contact dermatitis or dust mites (33).

2.1.3.3 Idiopathic chronic hand eczema

The distinct cause of CHE in twenty to twenty-six percent of patients can not be clearly explained. The condition exhibited without any history of atopy or any irritants/allergens exposure. Idiopathic chronic hand eczema tends to be associated with hyperkeratotic palmar eczema and on occasions plantar eczema (13, 23).

2.1.4 Clinical manifestation

The clinical manifestation of CHE is divers and the morphology tends to change depending on time.

In the acute stage, hand eczema typically presents with erythema, edema and vesiculation. As lesions become subacute or chronic, the morphology shifts to a more scaling form of the skin with often thicken, and frequently accompany with crackle or fissuring. The lesion usually affect both side and may include the palm or the back of the hands, or both areas. Nail changes may be seen in chronic disease which include loss of the cuticle, swelling of nail folds, ridging and thickening of the nail plate (13, 23).

Clinical variants of hand eczema include (13)

- Chronic fissured hand eczema
- Recurrent vesicular hand eczema
- Hyperkeratotic palmar eczema
- Pulpitis

- Interdigital eczema
- Nummular hand eczema.

2.1.4.1 Chronic fissured hand eczema

This characteristic of hand dermatitis is commonly found when the condition extends from months to years and defined as a dry, usually scaly eczema with an area of hyperkeratotic and fissure. The limited number of vesicle can be seen on the side of palm and fingers or palmar aspects of the hand (13, 23)(Figure 2.1).

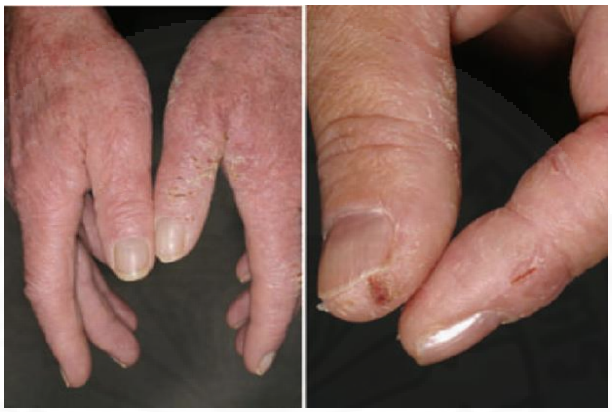


Figure 2.1 Chronic fissured hand eczema (13).

2.1.4.2 Recurrent vesicular hand eczema

Recurrent vesicular hand eczema is a repeated eruption of vesicles on the palmar area of the hands, the sides of the fingers, and can be also found on the plantar area of the feet and around the fingernails.

The eruption can last from weeks to months and the clinical manifestation can sometime present as chronic eczema (13). (figure 2.2)

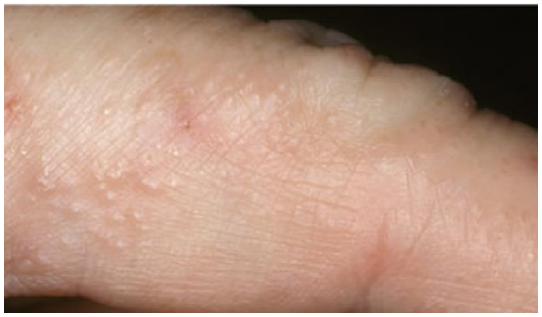


Figure 2.2 Recurrent vesicular hand eczema (13).

2.1.4.3 Hyperkeratotic palmar eczema

Hyperkeratotic type of hand dermatitis is defined as a well demarcated hyperkeratosis on the palms sometime with fissure and may extend to the palmar area of the fingers. Vesicular morphology is not present in any period of the disease. The lesion can also present on the sole of the feet.

The clinical presentation of hyperkeratotic variant can be separated from psoriasis by the absent of inflammation and psoriasiform scaling. Moreover, there is no nail changes found in hyperkeratotic palmar eczema (13).(Figure 2.3).

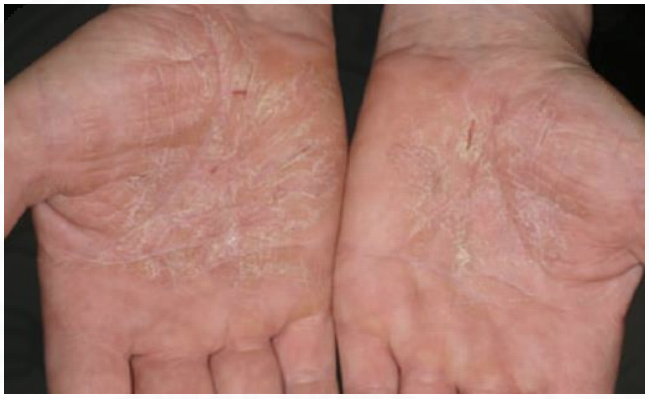


Figure 2.3 Hyperkeratotic palmar eczema (13).

2.1.4.4 Pulpitis

Pulpitis is a hyperkeratotic dermatitis which involve only on the fingertips and may be extended under the nails. Crackle and vesicle may sometimes present. It may affect all fingers but frequently present on the first and third digit of the hand (13). (Figure 2.4)

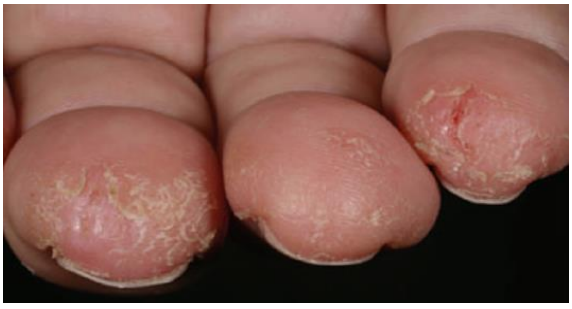


Figure 2.4 Pulpitis (13).

2.1.4.5 Interdigital eczema

It is an eczema that often present with erythema and scaling which commonly occur at the proximal aspect of interdigital area but infrequently present with vesicles (13) . (Figure 2.5).

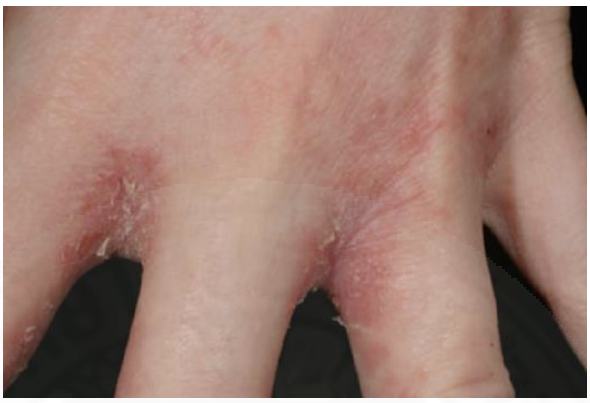


Figure 2.5 Interdigital eczema (13).

2.1.4.6 Nummular hand eczema

This type of eczema is located on the dorsal aspects of the hands or fingers. It is defined as a well circumscribed erythema lesion, commonly with hyperkeratosis, vesicles, and possibly present with serum oozing. Nummular eczema is frequently associated with secondary S. aureus infection (13). (Figure 2.6).

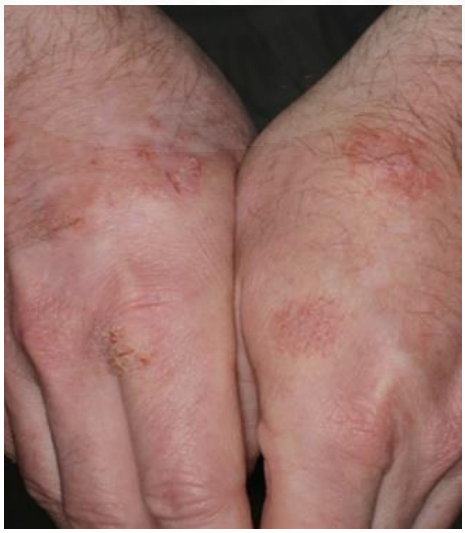


Figure 2.6 Nummular hand eczema (13).

2.1.5 Severity assessment

It is important for clinicians to evaluate the extent and characteristics of CHE thus this process can influence the management modality.

There are several tools for severity assessment of hand eczema including (34)

- The hand eczema severity index (HECSI)
- Physician Global Assessment (PGA) - Modified Total Lesion Symptom Score (mTLSS)
- The Osnabrueck Hand Eczema Severity Index (OHSI)
- Investigators' Global Assessment (IGA)
- The Photographic Guide
- The Dermatology Life Quality Index (DLQI)

2.1.5.1 The hand eczema severity index (HECSI)

The HECSI is a scoring method developed for the clinical evaluation of hand eczema which relies on the severity of clinical signs including 6 distinguish clinical signs (scaling, redness, thickening, edema, fissure, and vesicle) and on the total area involvement which distributed into five locations including wrist, dorsum of hand, palmar aspect of hand, fingertip and finger (except the tip).

The intensity of 6 clinical signs are graded as

0 : absent of lesion

1 : mild disease

2 : moderate disease

3 : severe disease.

The total affected area of both hands is given a score of 0-4

0 : 0%

1 : 1%-25%

2 : 26%-50%

3 : 51%-75%

4 : 76%-100%.

Finally, the total sum of the score for the involved area is multiplied by the total summary of the potency of each clinical morphology and the result is the HECSI total score which varies from 0 to 360 (35, 36). (Table2.1)

Table2.1 The hand eczema severity index (HECSI)

Clinical signs	(E)	(I)	(V)	(F)	(S)	(O)	Total clinical score	Extent (35)	HECSI Scores
Fingertips									
Finger (except tips)									
Palm of hand									
Back of hand									
Wrists									
								Total HECSI Score =	

Erythema(E) Infiltration/papulation(I) Vesicles(V) Fissures(F) Scaling (S) Oedema (O)
Modified from:(36)

2.1.5.2 Physician Global Assessment (PGA)-Modified Total Lesion Symptom Score (mTLSS)

PGA is a clinical assessment tools that determind the severity of hand dermatitis based on the intensity of clinical sign and percentage of the hand-surface involvement. It is a 5-level scale graded as clear, almost clear, mild disease, moderate disease, and severe disease.

The affected hand surface is defined as the area representing the more severely involved site (palm or dorsum) of the more involved hand and did not refer to the eczema localized to fingertips (37).Table2

The intensity of 6 clinical morphologies including erythema, scaling, hyperkeratosis/lichenification, edema, vesiculation, fissures, and even a subjective symptom as pain/pruritus are evaluated depended on the modified Total Lesion Symptom Score (mTLSS), ranging from 0 (absent) to 3 (severe) (37, 38). Table3

Table 2.2 The Physician Global Assessment (PGA). Modified from:(37)**.**

PGA Severiy	Features	Intensity	Area involved
Severe	Erythema, scaling, hyperkeratosis/ lichenification Vesiculation, oedema, fissure, pruritus/pain	At least 1 moderate or severe At least 1 severe	>30% of hand surface
Moderate	Erythema, scaling, hyperkeratosis/ lichenification Vesiculation, oedema, fissure, pruritus/pain	At least 1 mild or moderate At least 1 moderate	10-30% of hand surface
Mild	Erythema, scaling, hyperkeratosis/ lichenification Vesiculation, oedema, fissure, pruritus/pain	At least 1 mild At least 1 mild	<10% of hand surface
Almost clear	Erythema, scaling, hyperkeratosis/ lichenification Vesiculation, oedema, fissure, pruritus/pain	At least 1 mild Absent	<10% of hand surface
Clear	Erythema, scaling, hyperkeratosis/ lichenification Vesiculation, oedema, fissure, pruritus/pain	Absent Absent	Not detectable

Table2.3 Modified Total Lesion Symptom Score (mTLSS) Modified from:(37).

Parameter	Description of severity
Erythema	0 = Absent
	1 = Faint erythema
	2 = Prominent redness
	3 = Deep intense red color
Scaling	0 = Absent
	1 = Slight flaking over limited areas, mostly fine scales
	2 = Flaking over widespread area(s), coarser scales
	3 = Desquamation covering over 30% of the hand, with coarse thick scales
Lichenification/hyperkeratosis	0 = Absent
	1 = Mild thickening with exaggerated skin lines over limited areas
	2 = Palpable thickening over widespread area(s)
	3= Prominent thickening over widespread area(s) with exaggeration of normal skin markings
Vesiculation	0 = Absent
	1 = Scattered vesicles affecting up to 10% of hand, without erosion
	2 = Scattered or clustered vesicles affecting up to 30% of hand, without visible erosion or excoriation
	3 = High density of vesicles extending over large area(s), or with erosion or excoriation
Oedema	0 = Absent
	1 = Dermal swelling over less than 10% of hands
	2 = Definite dermal swelling over more than 10% of hand
	3 = Dermal swelling with skin induration over widespread area(s)
Fissures	0 = Absent
	1 = Cracked skin affecting a small area of the hand
	2 = Cracked skin affecting multiple areas of the hand and causing pain
	3 = One or more deep fissures and causing bleeding or severe pain
Pruritus/pain	0 = Absent
	1 = Occasional, slight discomfort a few times per day
	2 = Intermittent, causing discomfort frequently during the day
	3 = Persistent or interfering with sleep
1 = mild; 2 = moderate; 3 = severe.	

2.1.5.3 The Osnabrueck Hand Eczema Severity Index (OHSI)

OHSI is an assessment method for evaluate the clinical intensity based on morphology and involved site. The clinical sign include 6 morphologies which are erythema, papules, scaling, vesicles, infiltration, fissures and the involved site is evaluated based on the area of the hands affected by at least 1 clinical signs (38).

The extended area is divided based on which area are involved. Each affected area of each hand is given as 1/8 of the hand. Entirely involved palm is defined as 1/8, back of hand: 1/8, each palmar or dorsal site of the fingers: 1/8. The score for the total extended area is the combination of all affected areas on both hands. (Figure 2.7).

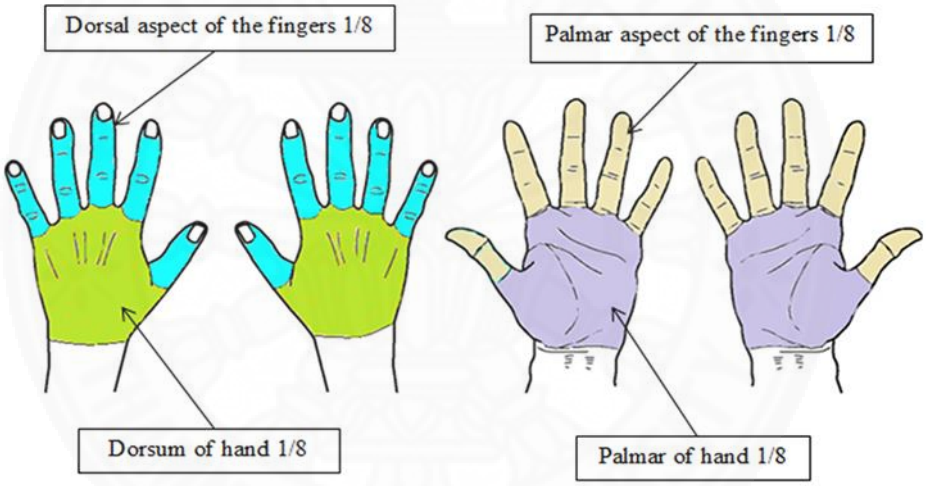


Figure 2.7 Extended area of The Osnabrueck Hand Eczema Severity Index (OHSI)

Except fissure, other clinical morphologies are classified based on the extended area mentioned above 0: no lesion, 1: spread ≥ 1/8, 2: spread between 1/8 - 2/8, 3: spread > 2/8.

Fissure are classified as 0 for no lesion, 1for small fissure size ≥ 5 mm with no hemorrhagic, 2: some small fissures or larger than > 5 mm fissures, 3: deep (hemorrhagic) fissure.

The summary of each clinical morphology indicated the total OHSI which ranges from 0 to 18 (38, 39). Table 4

Table 2.4 The Osnabrueck Hand Eczema Severity Index (OHSI)

Morphology	Extension area								Scores
	Lt.hand				Rt.hand				
	Palm of hand	back of hand	Palmar aspect of all fingers	Dorsum aspect of all fingers	Palm of hand	Dorsum of hand	Palmar aspect of all fingers	Dorsum aspect of all fingers	
Erythema[a]									
Scale[a]									
Papule[a]									
Vesicle[a]									
Infiltration[a]									
Fissures[b]	Characteristics of fissures								
Sum									

(a) Erythema, Scale, Papule, Vesicle and Infiltration are score due to the extension of the area involvement

0 : no lesion

1 : spread more than 1/8

2 : spread between 1/8 and 2/8

3 : spread > 2/8

(b) Fissure is scored due to its clinical and size.

0 : for no lesion

1 : for small fissure (≥ 5 mm) without hemorrhage

2 : some small flat or larger (> 5 mm flat fissures)

3 : deep (hemorrhagic) fissure

2.1.5.4 Investigators' Global Assessment (IGA)

IGA evaluate the severity of hand eczema based on the severity of clinical sign. It consists of 5 grades which defined as

0 : Clear or no lesion

1: nearly absent, only detectable scaling/redness without cracking

2: Mild intensity and/or mild cracking.

3: Moderate intensity and/or moderate cracking

4: Severe intensity: severe scaling and/or severe erythema, and/or severe cracking.

Both palmar and dorsum aspect of the hand are assessed together (38).

2.1.5.5 The Dermatology Life Quality Index (DLQI

DLQI is a non-complicated 10-question verified questionnaire that has confirmed to be beneficial for patients with hand dermatitis in term to evaluate health-related quality of life.

These 10 questions evaluate the physical, social and functional aspects of life affected by skin disease during the latest week. The scoring of each question is graded as follows;

3: Very much

2: A lot

1: A little

0: Not at all, Not relevant

In Question number 7, for the answer 'prevented work or studying' = scored 3

The summation of the score calculated from each question is the DLQI. A maximum score is 30 which means worst quality of life and a minimum of 0 which means best quality of life with respect to dermatological disease (38, 40, 41). (Figure 8). The interpretation meaning of the DLQI scores is as follows;(40, 41)

0 – 1 indicate no influence on patient's life

2 – 5 indicate minimal influence on patient's life

6 – 10 indicate moderate influence on patient's life

11 – 20 indicate very influence on patient's life

21 – 30 indicate extremely influenc on patient's life

Hospital No: ..... **Date:** .....

Name: ..... **Score:** .....

Address: ..... **Diagnosis:** .....

.....

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant	❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒		
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒

Please check you have answered EVERY question. Thank you.

Figure 2.8 Dermatology Life Quality Index (DLQI) (32).

2.1.5.6 The Photographic Guide

This tool was constructed by Coenraads et al. as a standard guide for validate the photograph of the hand dermatitis's clinical severity. This guideline distinguish the intensity of hand eczema based on the clinical finding and further categorized into 5 levels from clear to very severe then the severity was graded by the number from 0 (clear) to 4 (very severe) (42).

Four rows of photographs which collocated by the increase of clinical intensity were use as the template for patients to compare the severity of their hands and grade the intensity with the number of the row representing the severity of the veritable dermatitis (43). (Figure 2.9).

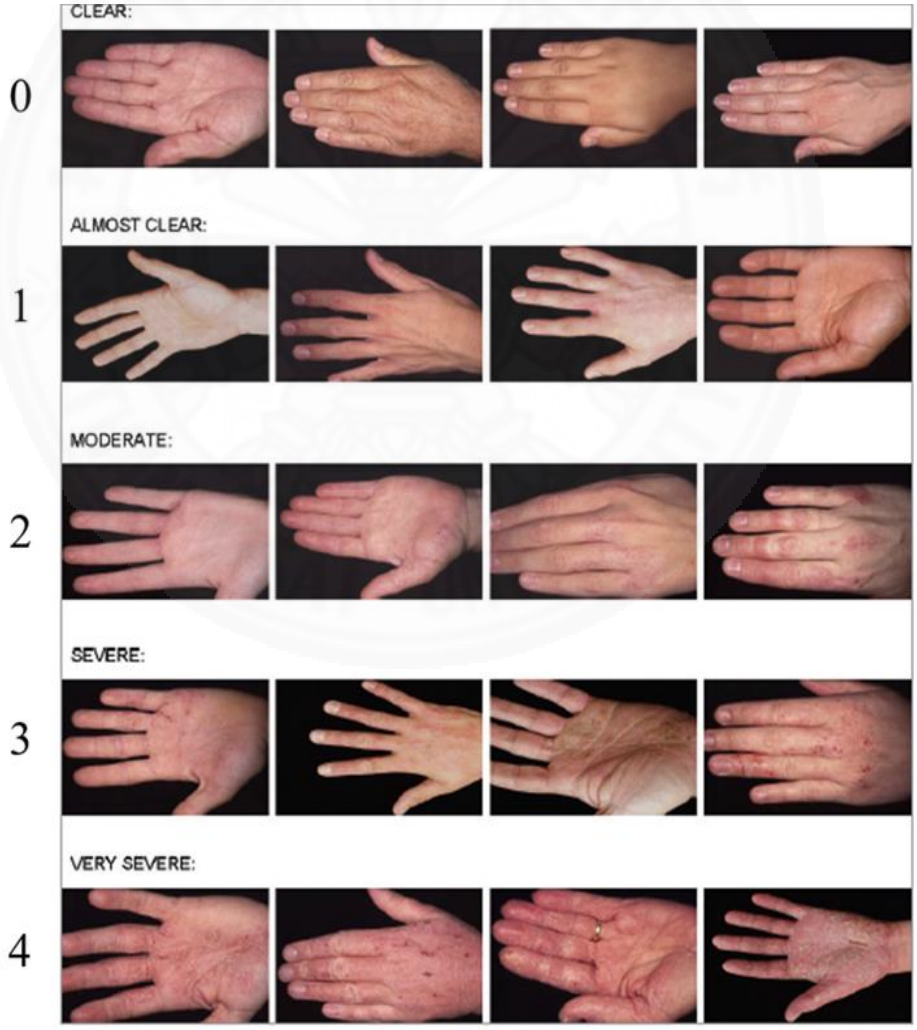


Figure 2.9 Modified Photographic guide (42, 43)

Overall, the 6 assessment tools mentioned above can similarly determine the clinical severity of hand dermatitis with a significantly positive association ($P < 0.001$). The strongest correlation demonstrated in the comparison between HECS Vs OHSI ($rs = 0.842$, $P < 0.001$), IGA Vs PG ($rs = 0.819$, $P < 0.001$), and HECSI Vs PGA-mTLSS ($rs = 0.812$, $P < 0.001$). The weakest relationship was found when compared the DLQI with all other scales (38, 44).

These tools are important for clinicians to evaluate the extent and characteristics of the eruption and the effect of the disease on patient's working ability and everyday activity, psychosocial functioning, and overall well-being (38).

2.1.6 Treatment

The management of CHE is complex and requires various treatment strategies depended on the causes of the eczema (eg: atopic, allergic, irritant), morphology and severity. Successful therapy mainly includes patient counseling, avoid contact with any irritant and allergen, skin protection method, and also the anti-inflammatory therapy both local and systemic.

Treatment options for chronic hand eczema (3).

1. Skin protection program such as patient education, irritant or allergic factor avoidance and substitution protection.
2. Topical therapies include emollients, topical corticosteroids, topical calcineurin inhibitors and other topical agents.
3. Systemic therapies include Acitretin, Alitretinoin, Azathioprine, Cyclosporine, Corticosteroids, Methotrexate.
4. Physical therapies include UVB, PUVA, iontophoresis.

2.1.6.1 Topical treatment

(1) Emollients

Emollients are required for various skin diseases which share characteristic of impair epidermal barrier dysfunction in term of prevention and treatment. Likewise, they are also prescribed for many occupational dermatoses. There are a number of emollients formulation. The components in each specific product can defined the efficacy and further impact on how to choose the product (45). Most emollients share similar effect which are increase the stratum corneum moisturization,

restore the lipid balance of the skin and as a consequent these improve barrier function, accelerate the healing of damaged skin, prevent itching and diminish the tendency to relapse.

Emollients have the potency to be an anti-irritated agent and were commonly prescribed for contact dermatitis cases. In an experimental study evaluated therapeutic effect of moisturizer on epidermal barrier function and hydration compared with control hands. In the study, one of participants' hands were treated with emollient before soaked into a 0.375% sodium lauryl sulphate solution while another hand served as control. By measure trans epidermal water loss and blood flow, the result reveal that the treated group demonstrated a significant therapeutic effect when compared to the control group. This can be concluded that moisturizer could possibly protect the skin from irritation and further increase barrier function (3, 46, 47).

However, there is a risk that using emollients may increase allergen penetration and irritants. A study conducted by Zachariae et al. in 2003, evaluated the skin response to allergen after using moisturizer on normal skin compared between right-left upper arm of the nickel-allergic volunteers. One arm of the participants was treated with emollient before underwent patch tests which contain 1% $NiCl_2$ aqueous solution while the other side left as control group. Trans epidermal water loss was also assessed together with the color and thickness of the skin by using bioengineering process. The outcome reveal that patch-test reactions intensity were increase on the emollient-treated side as demonstrate by clinical scoring, trans epidermal water loss and the thickness of skin while there is no significant different of any assessment method found in control group. This findings show that the use of lipid-rich moisturizers may influence the threshold of allergic response in patient who has already sensitized (48).

(2) Topical corticosteroids

Topical application of corticosteroids is considered as the mainstay treatment of CHE. In mild to medium degree of hand eczema, the skin lesion tends to be hyperkeratotic or commonly recurrence. As a consequence, a high or super potent topical corticosteroids is the recommended strength for the treatment.

Two clinical studies included an open randomized prospective study and a double-blind left/right comparison trial have demonstrated the effectiveness

of topical application of steroid. The first one is a double-blind left/right comparison trial which compared the clinical improvement of two different potency of topical corticosteroids, a strong potent (clobetasol propionate) and medium potency (flupredniden acetate) demonstrated that the application of higher potency topical steroid yielded an excellent therapeutic effect in CHE with also extend the relapse-free interval (49).

Due to its disadvantage, topical corticosteroids should be considered for short-term application. The adverse effects of topical steroid include, interfere repairmen of the stratum corneum causing skin atrophy and alteration of skin barrier, tachyphylasix and adrenal suppression (50).

Topical corticosteroid can possibly cause allergic contact dermatitis with the delayed allergic reactions being much more common than immediate reactions (with the prevalence estimated to be 0.1–0.3%). This condition should be awared in patients with CHE who does not response to the treatment. Topical corticosteroids can be uses once daily or twice a day in 2 to 4 weeks and for intermittent maintenance regimen is 2 - 3 times weekly, within 6 weeks and depended on the severity of eczema. For acute or eczema with vesiculation, cream preparation would be more suitable while ointment preparation should be used for chronic hand eczema (3, 13, 49, 51, 52). A double blind randomized clinical trial conducted with 44 participants reported that a daily application and twice a day application of topical corticosteroid found improvement in severity of hand eczema with decrease the VAS score and has no statistic significant differences in patients' quality of life evaluated by DLQI (51).

(3) Topical calcineurin inhibitors

Topical calcineurin inhibitors are approved to use in patients with atopic dermatitis that failed to response to topical corticosteroid. However, several studies demonstrate the effective outcome of these drugs in hand dermatitis. Apart from improving the clinical intensity of hand eczema, local used of calcineurin inhibitors also exhibited the ability to defer the recurrences of disease and may considered as a combined long-term treatment option for patient with chronic hand eczema (53-56).

Pimecrolimus appears to improve the clinical sign of dermatitis and can be substituted in the areas that topical corticosteroid might be

inappropriated to use (the face and neck) (4). A randomized, placebo controlled study compared the efficacy of a calcineurin inhibitor (pimecrolimus) with a vehicle cream conducted in 294 participants with mild to moderate CHE showed superior results for pimecrolimus (P = .033) with a low rate of application-site reactions (54).

However, there are others study that shown no significant differences between the treatment result. One study conducted with 652 mild-moderated chronic hand eczema patients randomized to treat with either overnight occlusion of 1% pimecrolimus or vehicle two times per day for 6 weeks. The result shown no statistically significant between the two group. The improvement was achieved in 29.8% of patients treated with pimecrolimus and 23.2% with vehicle (55).

In a single-center randomized controled trial which compare the therapeutic ability of 0.1% Tacrolimus with 0.1% mometasone furoate shown that more than 50% reduction of baseline eczema scores after both treatment ($P < 0.05$) and therefore the possibility of tacrolimus to be a rotational treatment regimen combining with corticosteroids for long-standing chronic hand eczema (53). Regarding to what mentioned above, tacrolimus is proved to be as effective as mometasone furoate in the treatment of hand eczema (53, 57). Only local adverse effects such as stinging or burning were reported in the study (56).

(4) Other topical treatment

- **Topical antibiotics and antiseptics**

Topical antibiotics and antiseptics such as chlorhexidine, clioquinol, are used to treat eczema with secondary infection, however they tend to cause allergic contact dermatitis. In this case, oral antibiotics are recommended (15).

- **Topical retinoids**

Bexarotene is a member of a retinoids subclass which has been licensed in cutaneous T-cell lymphoma both oral and topical form. In A phase I-II open-label randomized clinical trial demonstrated the efficacy of monotherapy 1%Bexarotene clearance of hands dermatitis. Around 90% of participants determined as disease clear and 79% reach at least 50% clinical improvement with well tolerated(58).

- **The tar-based products**

The tar-based products have an anti-inflammatory, antipruritic, and antiproliferative properties so it was used in subacute to chronic eczema (59, 60).

2.1.6.2 Systemic treatments

Systemic treatments, including oral corticosteroids, retinoids and immunosuppressants are indicated for refractory hand eczema or the hand eczema that persists after proper topical treatment for 8 weeks (61, 62). (Table 2.5)

Table 2.5 Most common used systemic treatments in chronic hand eczema. Modified from: (3).

Systemic treatment	Licensed for hand eczema	Benefit (Pros)	Harm (Cons)
Acitretin	No	One small trial show efficacy in hyperkeratotic dermatitis of the palms	Teratogenic, must be avoid during pregnancy
Alitretinoin	Yes	Three randomized controlled trials show efficacy in chronic hand eczema	Teratogenic, must be avoid during pregnancy
Azathioprine	No	No evidence of benefit in hand eczema	Hepatotoxicity, bone marrow suppression, increase toxicity in patient with thiopurine methyltransferase deficiency. Immunosuppression
Cyclosporine	No	Equivalent efficacy to betamethasone dipropionate. 12 months achieved at a dose of 3 mg/kg	Nephrotoxicity, hypertension, adverse effects on skin. Immunosuppression
Corticosteroids	No	Few convincing studies in hand eczema	Adrenal suppression, upper gastrointestinal symptoms, hypertension, increase risk of diabetes and osteoporosis
Methotrexate	No	Small controlled trials show efficacy in hand eczema	Liver toxicity; blood marrow depression

At present, the only systemic treatments approved in the treatment of CHE is alitretinoin, which may be considered a second-line option.

There is no other systemic treatment that approved and have a strong evidence of efficacy in the treating of hand eczema, most of them are prescribed off-label and have not been studied in randomized clinical trials (4, 15, 63).

(1) Systemic retinoids

- **Alitretinoin**

Alitretinoin binds to retinoid receptors which therefor exhibit the immunomodulatory and anti-inflammatory effects. It is licensed to use in severe CHE that fail to response or shown insufficient outcome to topical corticosteroids. In a phase III clinical study demonstrated the therapeutic efficacy of alitretinoin in CHE which conducted in 1,032 severe refractory hand dermatitis patients reported that around 48 % of patients in 30 mg alitretinoin treated group show completely cured or almost cured within three to six months compared to 17% ($P < 0.001$) in placebo group. A higher response rates found in hyperkeratotic variant and pulpitis more than those with vesicular eczema (33%). Adverse effects of alitretinoin are dose-dependent. The most frequent adverse effect is headache (10% at dose 10mg/d and 20% at dose 30mg/d), followed by flushing (1% at dose 10mg/d and 4% at dose 30mg/d), mucosal drying (2% at dose 10mg/d and 4% at dose 30mg/d). Common systemic adverse effect are hyperlipidemia, decreased thyroxine and thyroid stimulating hormone levels. Alitretinoin has a teratogenic effect that must not be used in reproductive aged women who cannot use or adhere to the adequate contraceptive methods (37)

Median time to recurrent of alitretinoin was 5.5 to 6.2 months (37) with the majority of cases relapsed after 3 months of discontinue the treatment (the rate of relapse 26%) (64). However, alitretinoin was reported to be effective in the re-treatmentation. In a randomized control study conducted in 117 relapse CHE patients demonstrated 80% benefit response after retreatment with alitretinoin was found in treatment group while 8% display in control group (65).

The dosage can be start with 30mg/d and can be reduced to 10 mg/d if there is any adverse reaction. The period of treatment is 24 weeks and should be stop if the eczema improved or if disease does not response (66).

- **Acitretin**

Recently acitretin is not yet approved in the treatment of CHE. The evidence for its efficacy is still limited. However, there were few studies reported the beneficial efficacy of acitretin in hand eczema. An open-label study compared the effect of acitretin 30 mg per day with placebo conducted in 29 patients with hyperkeratotic hand eczema. Approximately 51 % reduction of all clinical finding reported in the treatment group while 9 % reduction found in a control. Nevertheless, this study did not exclude psoriasis patients therefore, this may influence the statistical analysis and efficacy of the medicine (67).

Acitretin has a teratogenic effect as it is a retinoid so during the treatment and at least 2–3 years after discontinuation of the drug, patients need to have an adequate contraceptive method (67).

(2) Cyclosporine

Cyclosporine was considered for the treatment of refractory CHE that fail to response to other conservative treatment. Forty-one patients with refractory CHE were recruited into a randomized clinical trial which compared the efficacy of oral cyclosporine with 0.05 % betamethasone dipropionate cream after participants were randomly treated with either regimens for 6 weeks. The result found no significant difference between the two medications with 50 % reduction of disease intensity in cyclosporine group while 32 % reduction was found in steroid group. The minimum therapeutic period should be maintained for 6 months with suggested initial dose 2.5 to 5 mg/kg/ then taped off over approximately 3 months (15, 68).

Due to its serious adverse effect such as increase of blood pressure, nephrotoxicity and increase risk of infection, cyclosporine is indicated for short treatment period which is to be discontinued if patient fail to response in 8 weeks (3).

(3) Systemic corticosteroid

Systemic corticosteroid is effective in acute severe hand eczema and not recommend using as chronic maintenance therapy especially for more than 3 weeks on account of their long-term adverse reaction such as osteoporosis, glaucoma, HPA axis suppression and the risk of rebound effect after stopping the treatment. The usual dose for prednisolone is 0.5 to 1 mg/kg/d (3, 15).

(4) Azathioprine

There is no specific evidence nor any approval license for using azathioprine as the treatment for CHE even though it has been used effectively in treating atopic eczema and pompholyx. Patients are required regular blood checkup and measurement of TPMT levels before initial therapy and during treatment with azathioprine due to its serious side effect such as liver toxicity, subdue bone marrow, and accelerate the toxicity in thiopurine methyltransferase (TPMT) deficiency patients (3).

(5) Methotrexate

Low dose methotrexate has shown to be effective in CHE which can further reduce and eliminated the usage of oral corticosteroid. In a case report included 5 patients with severe refracturing pompholyx who suffered from corticosteroids' adverse reaction. Methotrexate 15-22.5 mg/wk displayed an improvement or even clearing the disease. However, methotrexate can induced remarkable side effects after chronic consumption which include pancytopenia and hepatitis thus patients need to be followed closely and appropriately adjusted dosage (69).

2.1.6.3 Physical therapies

(1) Photo-therapy

Physical therapies including UVB and PUVA are indicated in chronic hand eczema that refractory to first line treatment. The treatment of choice is psoralen plus UVA (PUVA) therapy, especially topical PUVA which is more preferable because of the adverse effects associated with oral psoralen. Phototherapy is effective in both hyperkeratotic and dyshidrotic eczema (4, 70).

UV-B phototherapy has also proven to be effective in the treatment of hand eczema. 15 patients with chronic hand eczema of dry and dyshidrotic types were treat with local narrowband UVB(TL-01) compare with paint-PUVA in a prospective, comparative study based on a left to right comparison pattern by Sezer E et al. The patients were randomly treated with either local narrowband UVB (TL-01) or paint-PUVA three times a week for 9 weeks. The result was statistically significant decrease in the mean clinical score in both group and no difference between the two treatment which can be concluded that treatment with local narrowband UVB is as

effective as paint-PUVA in patients with chronic hand eczema of dry and dyshidrotic types (71).

Other study performed in 35 patients whose hands were randomly treated with either UVB or PUVA. One hand was kept as control side while another was exposed to phototherapy (UVB or PUVA). This study demonstrated that PUVA was superior to UVB therapy. all patients treated with PUVA are cleared of the dermatitis while there was no any skin lesions in the UVB treated sides found completely cured(72).

UV therapy, especially bath and paint PUVA, were reported to have local side effects which are erythematous and burning of skin (3).

(2) Iontophoresis

Iontophoresis refer to the method that allowing ionized particles to surpass the normal skin barrier by consigning the electrical current through the tap water or normal saline (0.9%NSS) soaked skin. This method has been successfully applied in topical drug delivery including the treatment of focal hyperhidrosis especially on the palms or soles which thought to be one of the an intensify factor for pompholyx. Other usages of iontophoresis include fungal infection of nail plate and local treatment of inflammation (73, 74).

Tap water iontophoresis was used to treat patients with palmar hyperhidrosis in a study by Wollina et al. The result is that patients who are treated with iontophoresis had a non-statistical significantly faster clearing of disease ($p > 0.05$). However, a highly significant different of the disease-free interval was found between the iontophoresis treated group and controlled ($p < 0.0001$). In conclusion, galvanization with tap water iontophoresis seem capable in control inflammation and prolongs the disease-free interval of hyperhidrotic palmoplantar dermatitis (75).

2.1.6.3 Skin protection program

Hand eczema has a multifactorial etiology and tend to be chronic and burden for patients' life. Prevention is important for the management of hand dermatitis fyrthermore, patients also need the education about avoidance of precipitating factors and the knowledge of epidermal barrier defects should also be considered.

The strategies of prevention can be distinguish into primary, secondary, and tertiary prevention method (62).

(1) Primary prevention

The primary prevention's most essential gold is to reduce the incidence of hand eczema in healthy population. The strategies include avoidance or substitution of harmful substances through legislative change on threshold values, application of personal protection equipment for instance gloves and barrier creams, identification of susceptible individuals through questionnaires and/or patch testing and education programs at the workplace, which have proven to be both beneficial and cost-effective(76).

(2) Secondary prevention

Secondary prevention is indicated when eczema is already present on the hands. The objective of secondary prevention is to detect early skin changes in order to rapidly execution corrective measures and inform the patient about hand eczema, its treatments, about lifestyle changes such as skin care, avoidance of irritants/allergens, and the use of protection measures (4, 77, 78).

In a randomized, observer blinded clinical trial which compare the influence of treatment with secondary prevention program (Include on individual counselling and skin care education) with the usual treatment modality on 255 healthcare-provider who have self-reported hand dermatitis. The result show significantly improved of clinical intensity and quality of life in the intervention group (97%, $P<0.001$) (79).

(3) Tertiary prevention

Tertiary prevention is indicated in patients with CHE and/or severe dermatitis of the hands that multiple treatments and also secondary prevention strategies have proven to be ineffective. The aim of tertiary prevention is to reduce the severity of disease, shorten sick leave duration, reduce the use of steroid and improve patient quality of life. The management is a multidisciplinary approach which may required dermatologist, health educational and psychological expert in such cases (80).

2.2 Topical vitamin D analogues

2.2.1 Introduction

Topical vitamin D analogues (Calcipotriol) developed from a synthetic modified side chain of 1α, 25- dihydroxyvitamin D3 (81) and was widely used as an alternative treatment for adult psoriasis. However, it also prescribed off-label to treat other inflammatory diseases that share several pathogenic characters (impaired differentiation and increase proliferation of keratinocyte) and has been reported to achieve beneficial effect as well (8, 9).

2.2.2 Structure

Calcipotriol is synthesized from a nuclear hormone called 1α, 25-dihydroxyvitamin D3 (1a,25(OH)2D3) by modifying the side chain into cyclopropane ring structure with aim to enhance the biologic properties of the original hormone for a potential therapeutic usage and to amend its hypercalcemic effect (81). (figure 10).

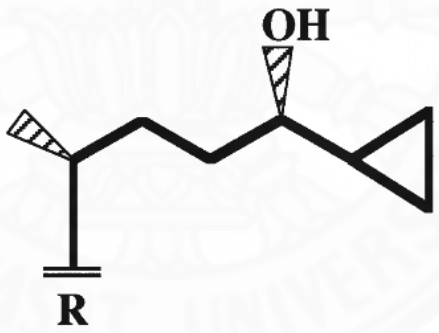


Figure 2.10 Structure of Calcipotriol (81)

2.2.3 Mechanism of actions

Calcipotriol specifically bind to the vitamin D receptor (VDR) which display similar properties compared with various steroid receptors including the glucocorticoid receptor, estrogen receptor and thyroid receptor. It also functions as a heterodimer to the retinoic receptor (RXR) presenting on keratinocyte and lymphocyte. The VDR - vitamin D3 complex then bind to specific promoter region of l, 25-dihydroxyvitaminD3 (Calcitriol) target gene which further regulate the transcription of

various genes therefore, modulate the epidermal proliferation, induce cellular differentiation and inhibit inflammatory effect (5).

Apart from binding to VDR on keratinocyte, vitamin D analogue also acts on melanocytes, monocytes, Langerhans cells, macrophages, fibroblasts, endothelial cells, and activated T cells which in charge of inflammatory reactions therefore decrease and inhibit the production of inflammatory mediators especially IL-1, IL-2 and IL-6. This resulting in inhibits T-cell proliferation, inactivate T-cell by swishing to CD8 suppressor cells, decrease the release of IFN-γ from mononuclear cells and also reduce infiltration of neutrophils and dermal cellular infiltrate (8, 82). In addition, calcipotriol increases the levels of epidermal growth factor both TGF-β1 and β2, therefore inhibit the epithelial cell growth and promote antiproliferation effect of keratinocyte (82).

2.2.4 FDA-approved indications

Calcipotriol has been approved for the topical treatment of psoriasis vulgaris, including plaque type psoriasis both in adults and children since 1994 (83). It may also be used in combination with systemic acitretin or cyclosporine in adult.

2.2.5 Non-FDA approved use

Apart from psoriasis, calcipotriol was reported to accomplish considerable beneficial therapeutic outcome in the treatment of other inflammatory dermatoses which shared the characteristics of increase keratinocyte proliferation and impaired differentiation

In a literature review of total 36 papers reported the potential of calcipotriol in skin diseases apart from psoriasis that shared the same pathologic character of impaired keratinocyte differentiation or increased epidermal proliferation, and activation of T lymphocyte. Calcipotriol also demonstrate an anti-inflammatory effect and take an essential part on many inflammatory skin diseases. Although most of the studies are case report and observational studies with others small RCTs which may not provide a strong statistical evidence, it can be implied that calcipotriol may be considered as an effective treatment in diseases with defect in epidermal differentiation or increase keratinocyte proliferation. Yet, their value can be further use for hypothesis generating and RCTs planning (8).

Another systematic literature review conducted in 2014 which invlove total 165 papers revealed the off-label treatment of other skin diseases apart from psoriasis by applying topical vitamin D derivative. The result shown that a monotherapy of calcipotriol demonstrated a moderate to strong recommendation in the treatment of many disease with a pathogenic feature of hyperkeratotic and hyperproliferative disorders such as disseminated superficial actinic porokeratosis, confluent reticulated papillomatosis, ichthyoses, polymorphous light eruption morphea, prurigo nodularis and Palmoplantar eczema (9).

There was a clinical case reported demonstrated the therapeutic effect of topical vitamin D3 derivative (calcipotriol 50 µg/g and maxacalcitol 25 µg/g ointments) in 5 hyperkeratotic palmoplantar dermatitis patients. The result showed a certain beneficial effects with the lesions almost disappeared in 4 patients after 2 to 8 weeks of treatment and highly improved in 1 patient after 7 weeks of treatment (11).

2.2.6 Contraindication

Calcipotriol contraindicated in patients who have a history of hypersensitivity to any components of the preparations. It should not be used by patients with exhibit hypercalcemia or evidence of vitamin D toxicity and should not be used on the face (82).

2.2.7 Adverse reaction

Treatment with calcitriol ointment in the recommended amounts, not more than 100g per week either short-term or long-term treatment or around 30 g per week for 1 year does not result in changes of laboratory values. The most common side effect after prolonged or excessive application is skin irritation and rarely hypercalcemia in patients with concomitant renal impairment.

Only local adverse reactions were mostly found after topical application of. Such irritation like burning or stinging sensation restrict the use of vitamin D analogues on the face and intertriginous areas. About 15% of the treated patients develop lesional/perilesional irritation within the first few weeks after medical application but during long-term usage, there was no any adjuctive irritation found and only l-2% of patients stop treatment for this reason. Erythema and scaling are present in more severe cases (81, 82).

CHAPTER 3
RESEARCH METHODOLOGY

3.1 Research questions

3.1.1 Can calcipotriol be an alternative treatment of chronic hand eczema?

3.1.2Can calcipotriol be a safe treatment of chronic hand eczema?

3.2 Statement of hypothesis

The severity of chronic hand eczema in calcipotriol ointment – treated group is significantly decrease after 8 weeks therapy when compared with the desoximetasone ointment – treated group.

3.3 Specific objectives

1.4.1 The primary objective is to assess the effectiveness of calcipotriol ointment in the treatment of chronic hand eczema.

1.4.2 The secondary objective is to assess adverse reactions of calcipotriol ointment in in the treatment chronic hand eczema.

3.4 Conceptual framework

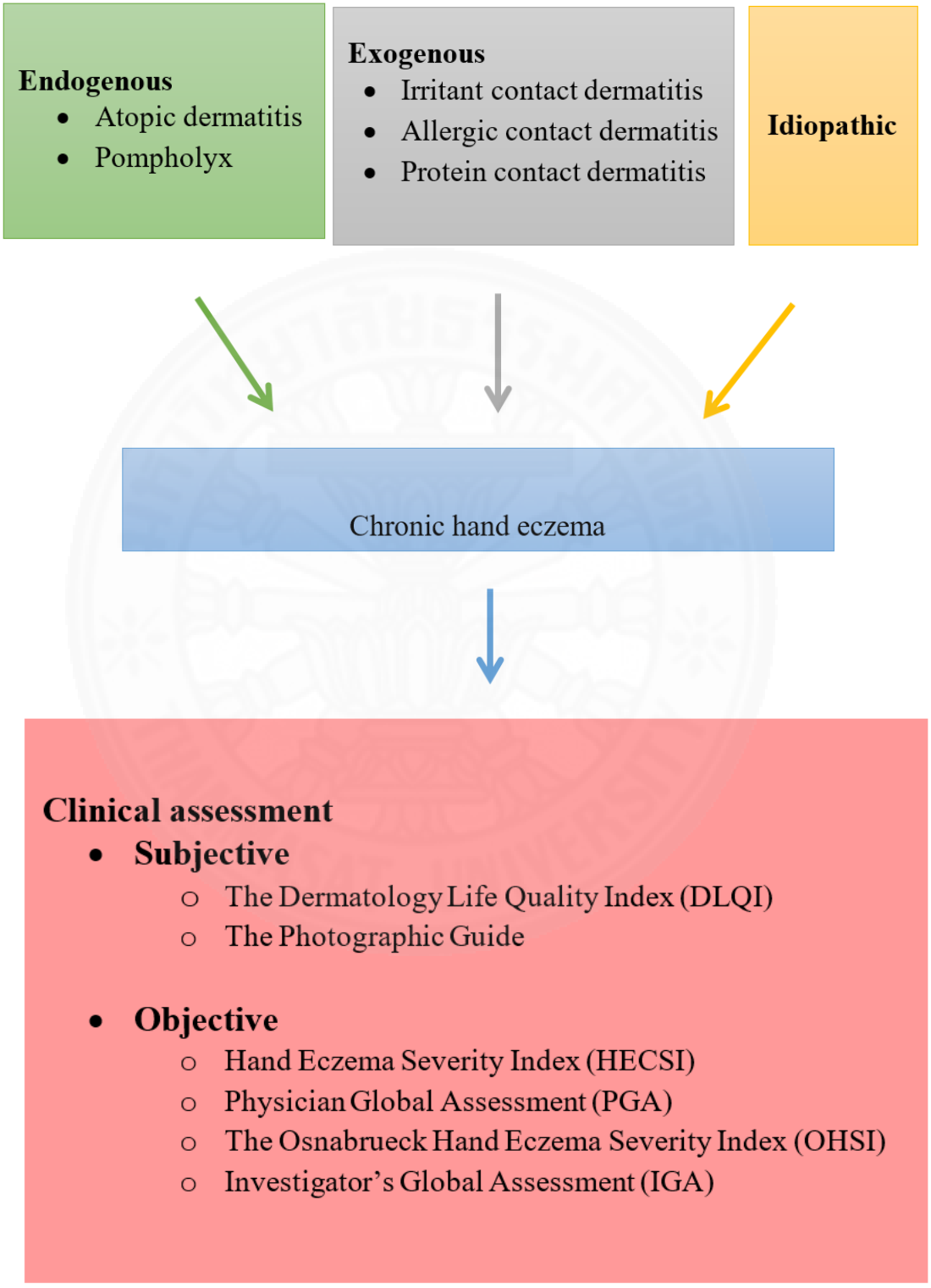


Figure 3.1 Conceptual framework

3.5 Significance of the research

Chronic hand eczema is a common dermatologic condition which affects all age groups and has a great impact on health, economic and psychologic aspect on individuals. Most cases of hand eczema are complex and difficult to manage due to its multifactorial etiologies. Many treatment modalities have been applied for the treatment of CHE, including skin protection program (patient education and avoidance of irritant or allergic factors), topical treatment like topical corticosteroids alone or together with a keratolytic medication like topical retinoid, emollients, calcineurin inhibitors) and even systemic treatment (systemic corticosteroid, methotrexate, azathioprine etc.) and physical therapy (UVB, UVA), however the efficacy of those treatments are limited and prone to induce side effects.

Calcipotriol, topical vitamin D analogues, specifically binds to the vitamin D receptor (VDR) presenting on keratinocytes, melanocytes, and various inflammatory cells thus, its actions can modulate the epidermal proliferation, influence keratinocyte differentiation and inhibit inflammatory effect. Calcipotriol was approved to use in the treatment of adult plaque type psoriasis and was reported to achieve beneficial effect in other inflammatory dermatoses which included palmoplantar keratosis. A twice daily of topical vitamin D analogues has been reported to have excellent therapeutic effect on chronic hyperkeratotic hand eczema in a pilot study however it still needs further studies to give stronger statistical evidence. Therefore, this randomized double blind comparison trial is designed to assess the effectiveness of calcipotriol ointment in the treatment of chronic hand eczema. Total 22 patients who meet the inclusion criteria are recruited into the study and undergo patch test to exclude the contact dermatitis, then their hands will be randomized to be treated with either calcipotriol or desoximetasone twice daily and evaluate the result with HECSI, the quartile grading score and photograph taking at the 2^{nd}, 6^{th}, 8^{th} and 12^{th} week. Any adverse reaction will be recorded during the experiment.

We hope this randomized controlled trial could further validate calcipotriol as another alternative option to treat chronic hand eczema in the future.

3.6 Operational definition

Chronic hand eczema is defined as an eczematous process that exclusively or primarily involves hands which exhibited at least 3 months or relapses at least two times a year despite an adequate treatment and treatment adherence

3.7 Ethical considerations

Patients will be explained in detail regarding the objectives, methods, expected benefits of the research and probable side effects (eg: scaling, stinging, redness, edema) during the study treatment and the voluntary nature of the study, then sign the inform consent form. All patients are rightful and free to withdraw from the study and continue the standard treatment.

3.8 Limitation

The limitations of our study are a small number of participants and short period of follow-up to determine relapses. However, in most of the cases, the lesions are tended to be less severe in every follow up and incline to be more improved even after the treatment period.

3.9 Expected benefits & applications

3.9.1 To knows the effectiveness of calcipotriol ointment in chronic hand eczema compared to the standard regimen.

3.9.2 To knows the adverse reactions of calcipotriol ointment in chronic hand eczema

3.10 Obstacles and solving strategies

Small number of patients lost to follow up mostly due to working time and unable to contact. However, most of the lost follow up patients are having an

improvement of their hand eczema. In order to solve this problem, the relationship between doctor and patient was improved. Moreover, the benefit of the treatment itself were significantly make patients want to continue the treatment.

3.11 Research design

This study was designed as a prospective, randomized, double-blinded, intraindividual, right-left comparative trial. The protocol was approved by Thammasat University Institutional Review Board. It was conducted in the outpatient unit of Thammasat University Hospital and Thai Tobacco Monopoly Hospital during September 2016 to February 2017. Informed consent was signed by an individual participant prior the enrollment.

3.12 Study sample

3.12.1 Target population

3.12.1.1 Inclusion Criteria

(1) Symmetrical chronic hand eczema (Duration > 3 months or Recurrent ≥ 2 episodes / year)

(2) Age ≥ 20 years

(3) Mild to moderate PGA severity

(4) Subjects are able to sign inform consent form

3.12.1.2 Exclusion Criteria

(1) Subjects with others dermatologic condition of the hand

(2) Known allergy to calcipotriol or desoximetasone ointment

(3) Use of topical corticosteroid within the last 2 weeks

(4) Use of systemic treatment within the last 4 weeks

(5) For female: pregnancy or lactation

3.12.2 Sample size and sample size calculation

By using G*Power 3.1.7 program, 22 patients need to be recruited in the study

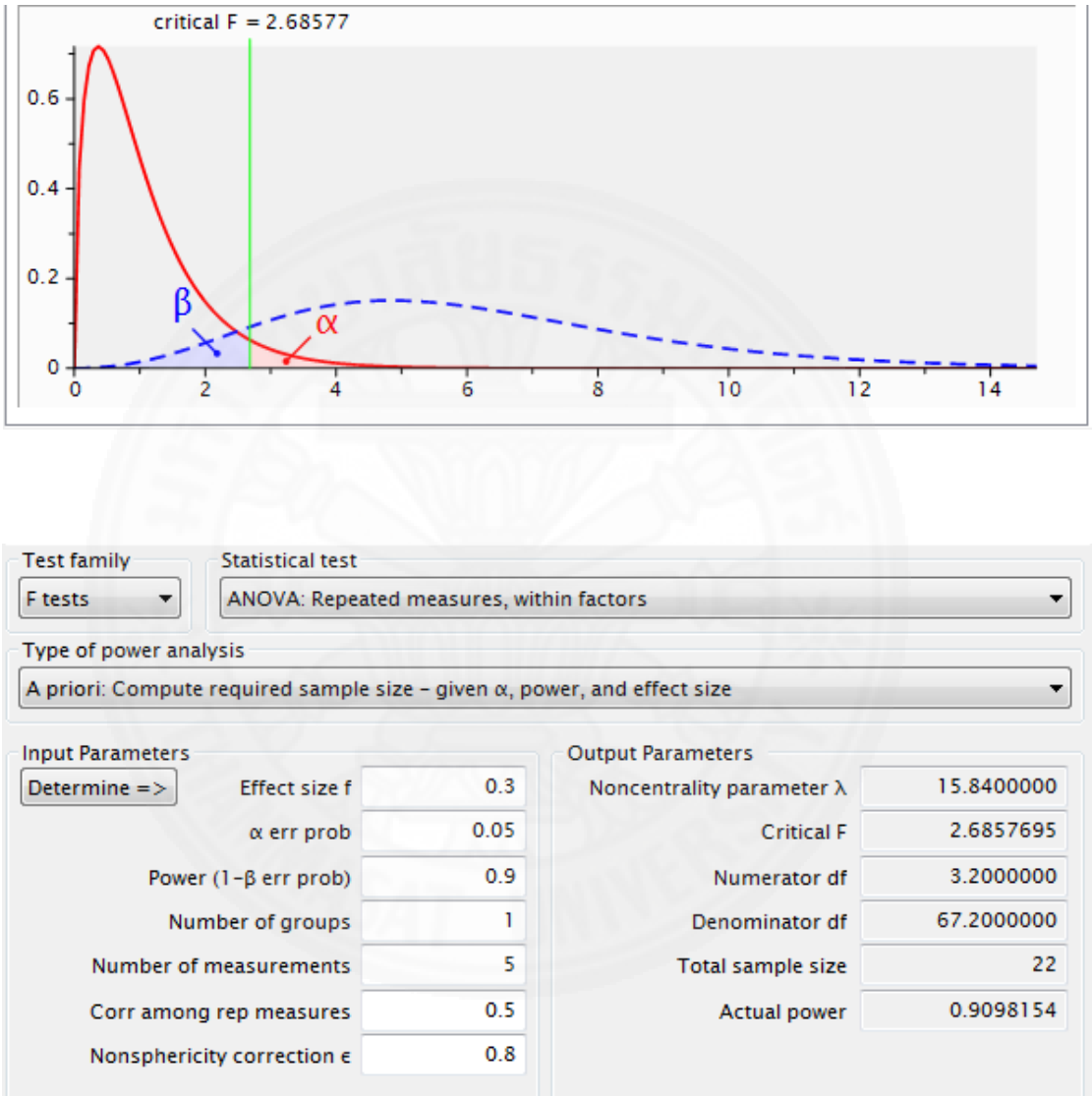


Figure 3.2 Calculation of sample size by G*Power 3.1.7 Program

3.13 Materials and methods

- Recruiting patients who reach an inclusion criteria.
- Patients will be explained in detail regarding the treatment duration, the need for regular follow-up, probable side effects (eg: scaling, stinging, redness, edema) during the study treatment and the voluntary nature of the study, then sign the inform consent form.
- Recruited patients will undergo patch test and will be excluded if the results are positive with relevance.
- Patients' hands will be randomized to be treated with either calcipotriol ointment or desoximetasone ointment using computer randomization (both patients and investigator are blinded to the type of treatment).
- Before start the treatment, pre-treatment photographs are taken and patients will be assessed the clinical severity score using HECSI by dermatologist.
- Patients will be assessed the clinical severity using HECSI by dermatologist and also undergo self-evaluation by using quartile grading scale every visit (2^{nd} ,6^{th}, and 8^{th} week) until the end of treatment period.
- All the patients are advised to apply the ointment (calcipotriol and desoximetasone ointment) only at the lesion on each hand by using cotton tip (the cotton tip will be used one time and disposed) twice daily.
- All the patients are advised to avoid others topical treatment or any cosmetic on their hands along the study period.
- After discontinuing the treatment, all the patients were treated with only petrolatum ointment on both hands for 4 weeks and were assessed the severity of their hands again for any relapse

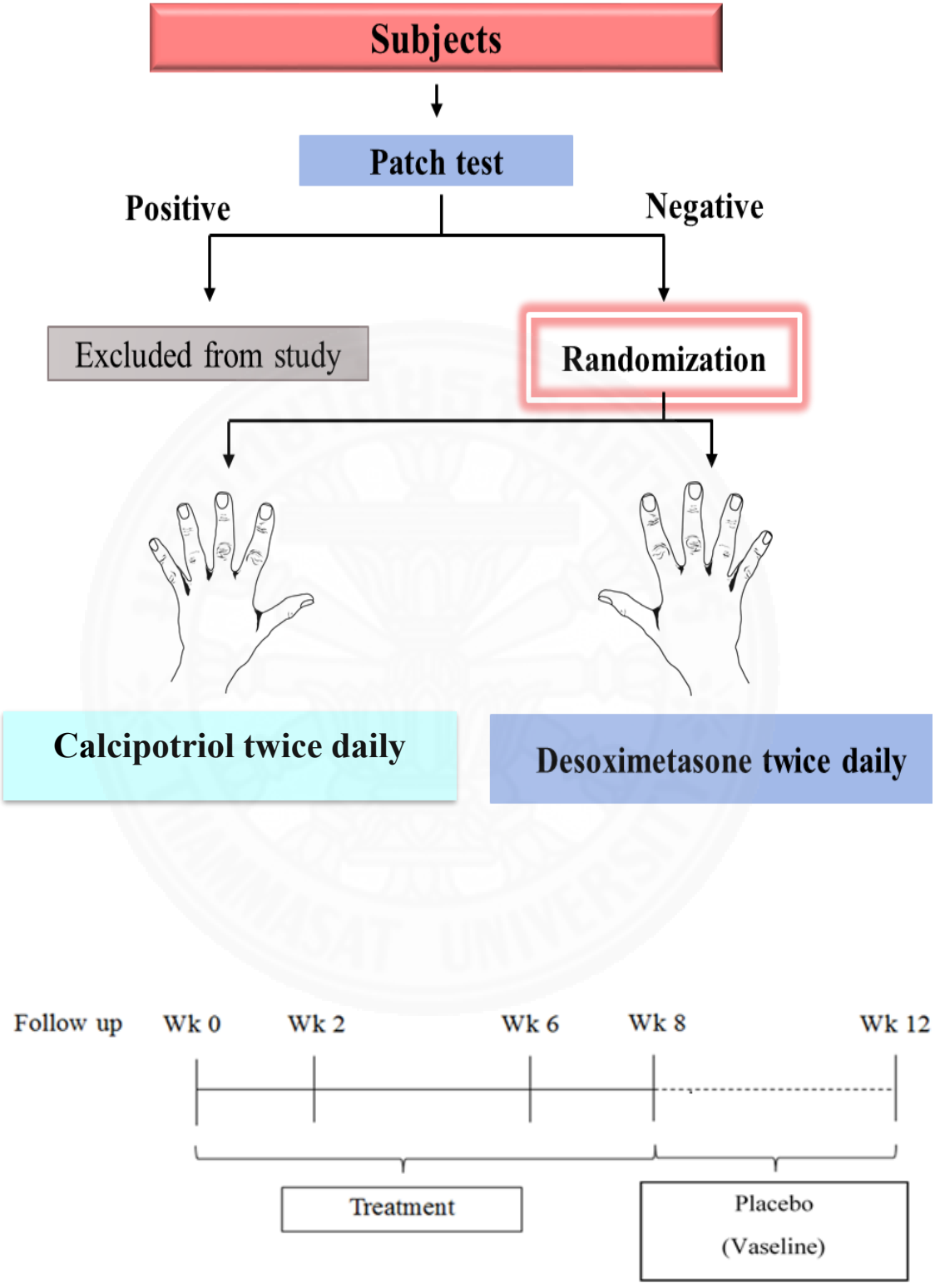


Figure 3.3 Material and method

3.14 Outcome measurement

Table 3.1 Outcome measurement

Tools	Treatment				F/U
	Baseline	2nd week	6th week	8th week	12th week
PGA	✓				
Photographs	✓			✓	✓
HECSI	✓	✓	✓	✓	✓
Dermatologist assessment		✓	✓	✓	✓
Patient self-assessment (Quartile grading score)		✓	✓	✓	✓
Adverse effects		✓	✓	✓	

3.14.1 Objective assessment

3.14.1.1 PGA

Patients aged more than 20 years old diagnosed with CHE of both hands with mild to moderate physician global assessment (PGA) severity (34) were included into this study.

3.14.1.2 Photographs

The series of clinical photographs of both treated hand and controlled site were taken by standard digital camera (Mirrorless, PEN E-P5, Olympus, Tokyo, Japan) at baseline, the end of treatment period and 4-week follow-up visit

3.14.1.3 HECSI

Clinical evaluation was assessed by single blinded-investigator at baseline and at every visit using the hand eczema severity index (HECSI) score. The HECSI is calculated depended on the severity of clinical signs including six different clinical presntations (redness, scaling, infiltration, edema, fissures, and vesicles) and on the total area involvement which distinguish into 5 locations including fingertips, fingers, palms, back of hands, and wrists). The intensity of 6 clinical signs

are graded on the following scale: 0, no skin changes; 1, mild disease; 2, moderate disease; 3, severe disease. For the extent of clinical symptoms, the affected area of each hand is given a score from 0 to 4 as follows: 0, 0%; 1, 1-25%; 2, 26-50%; 3, 51-75%; 4, 76-100%. Finally, the total sum of the score for the extent at each area is multiplied by the total sum of the intensity of each clinical sign and the result is the HECSI total score which varies from 0 to 360 (34, 36).

3.14.2 Subjective assessment

Patients will be interviewed and asked to evaluate the severity of their hands using visual Analogue Scale before treatment and Quartile grading score every visit. The visual Analogue Scale scored from 0 to 10 which "0" refer to no symptom and "10" refer to the most severe symptom. Quartile grading score will be assessed for the improvement. The score ranges from 0 to 4 which refer to no improvement, 1-25%, 26-50%, 51-75%, and 76-100% improvement, respectively.

3.14.3 Adverse effects

The severity and duration of possible adverse effects related to treatment including erythema, burning or stinging and scaling will be assessed at every visit.

3.14.4 Case record form

All the data will be enrolled in case record form shown in the appendices.

3.15 Data analysis

All data were analyzed using a statistical analysis software (SPSS version 21.0; SPSS Inc, Chicago, IL, USA). The statistical significance of mean total HECSI changed compared with baseline within both treated sides was determined by using Wilcoxon matched pairs test. Mann-Whitney U-test was used to compare mean HECSI changed from baseline between two independent group (Calcipotriol and Desoximetasone - treated side). The clinical improvement assessed by quartile grading score from patients were also analysed by Mann-Whitney U-test.The statistical significance was defined by p-value <0.05.

CHAPTER 4
RESULTS AND DISCUSSION

4.1 Study population

At the beginning, 21 patients were recruited into the study. After making and appointment for patch testing, five of them were unable to complete the patch test so there were 16 patients left to continue the study. However, after patch testing was done, three patients out of 16 were positive for patch test with relevant history so the total participants who met the inclusion criteria were enrolled and completed the study would be thirteen (seven females and six males).

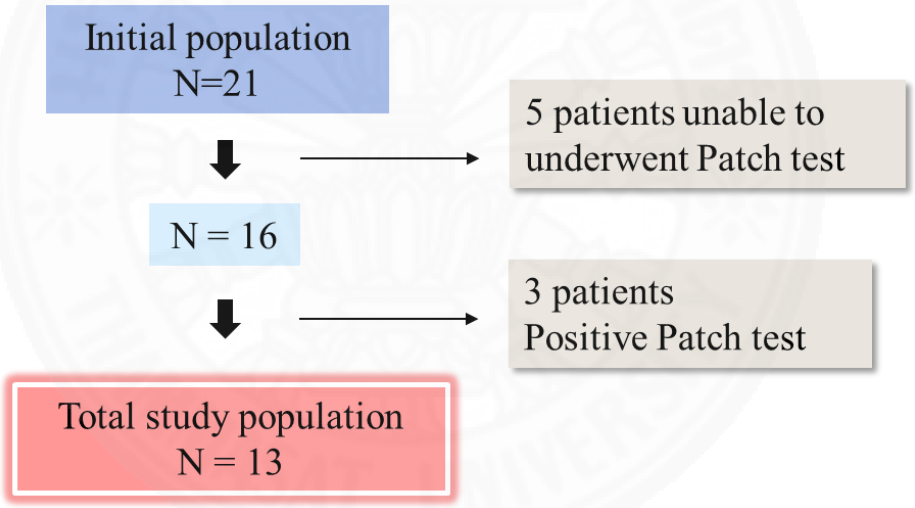


Figure 4.1 Study population

The mean age of the subjects was 48.62 ± 11.51 years with a range from 26 to 66. The overall duration of disease was 8.62 ± 2.9 months. Clinical variants of patients' hands were mostly hyperkeratotic palmar eczema which was found in 61.54% of the subjects followed by hyperkeratotic concomitant with chronic fissured hand eczema and pulpitis which were noticed equally at 15.38% while recurrent vesicular palmar eczema was noted in 7.70% of the subjects. Six participants were identified as mild PGA severity while the rest were moderate PGA severity. (Table 4.1- 4.3).

Table 4.1 Baseline characteristics of population

Subject	Sex	Age	Clinical variant	Duration (mo)	Baseline PGA	Previous treatment	Side effect	
							Calcipotriol	Desoximetasone
No.1	F	59	Hyperkeratotic + Chronic fissured hand eczema	15	moderate	Steroid + Emollient	mild scaling	mild stinging, mild dryness
No.2	M	54	Hyperkeratotic palmar eczema	7	mild	Steroid + Emollient	mild scaling	mild stinging, mild dryness
No.3	F	26	Pulpitis	7	mild	Steroid + Emollient	moderated dryness, mild scaling	mild dryness, mild crackle
No.4	M	41	Hyperkeratotic palmar eczema	6	moderate	Emollient	mild scaling	mild stinging and dryness sensation
No.5	F	41	Pulpitis	5	mild	Emollient	mild scaling	none
No.6	F	61	Hyperkeratotic + Chronic fissured hand eczema	10	moderate	Steroid + Emollient	mild scaling	mild dryness
No.7	M	62	Hyperkeratotic palmar eczema	6	mild	Steroid + Emollient	moderated scaling and mild stinging	mild stinging, mild crackle
No.8	M	51	Hyperkeratotic palmar eczema	10	moderate	Steroid + Emollient	mild dryness, mild scaling	mild dryness
No.9	F	43	Recurrent vesicular hand eczema	13	moderate	Steroid + Emollient	moderated crackle and scaling, mild stinging	mild dryness, mild erythema
No.10	F	45	Hyperkeratotic palmar eczema	8	mild	Emollient	mild scaling	mild dryness
No.11	M	46	Hyperkeratotic palmar eczema	7	mild	Emollient	mild scaling	mild dryness
No.12	F	37	Hyperkeratotic palmar eczema	10	moderate	Steroid + Emollient	mild scaling	mild dryness
No.13	M	66	Hyperkeratotic palmar eczema	8	moderate	Steroid + Emollient	moderated scaling	mild erythema

Table 4.2 Hand eczema severity index (HECSI) and Quartile grading scale of patients

Subjects	HECSI Calcipotriol					HECSI Desoximetasone					QGS Calcipotriol Pt.					QGS Desoximetasone Pt.				
	Wk 0	Wk2	Wk6	Wk8	Wk12	Wk 0	Wk 2	Wk6	Wk8	Wk12	Wk2	Wk6	Wk8	Wk12		Wk2	Wk6	Wk8	Wk12	
No.1	46	31	15	6	18	48	30	29	9	22	2	3	3	3		1	2	4	2	
No.2	28	20	6	3	4	25	18	6	5	7	2	3	4	4		3	3	4	4	
No.3	25	24	10	6	8	26	27	12	14	20	2	3	4	3		1	2	2	2	
No.4	48	33	12	11	8	34	23	7	4	7	2	3	3	3		2	3	4	3	
No.5	23	0	0	0	0	21	3	0	0	0	4	4	4	4		3	4	4	4	
No.6	53	34	10	8	10	64	40	22	9	12	1	3	4	4		2	3	4	4	
No.7	28	28	26	11	14	26	24	21	10	14	1	1	3	3		1	1	3	3	
No.8	30	17	12	8	16	44	28	15	12	17	2	3	4	3		2	3	4	3	
No.9	48	42	30	21	21	35	23	8	11	12	1	2	3	3		2	3	3	3	
No.10	18	14	13	8	10	27	21	19	14	16	2	2	4	3		2	3	4	3	
No.11	21	18	12	6	6	13	11	6	3	6	2	3	4	4		2	2	4	4	
No.12	42	32	21	10	13	32	21	15	11	12	1	2	4	3		2	3	4	3	
No.13	58	38	20	15	15	53	22	12	6	10	1	2	4	3		3	4	4	3	

Table 4.3 Characteristics of the Study Population

Characteristics	Percent
Sex	
Female	53.84
Male	46.15
Baseline PGA	
Moderate	53.85
Mild	46.15
Previous Treatment	
Topical steroid+emollient	69.23
Emollient	30.77
Clinical variants	
Hyperkeratotic palmar eczema	61.54
Hyperkeratotic concomitant with Chronic fissured hand eczema	15.38
Pulpitis	15.38
Recurrent vesicular hand eczema	7.70

4.2 Efficacy

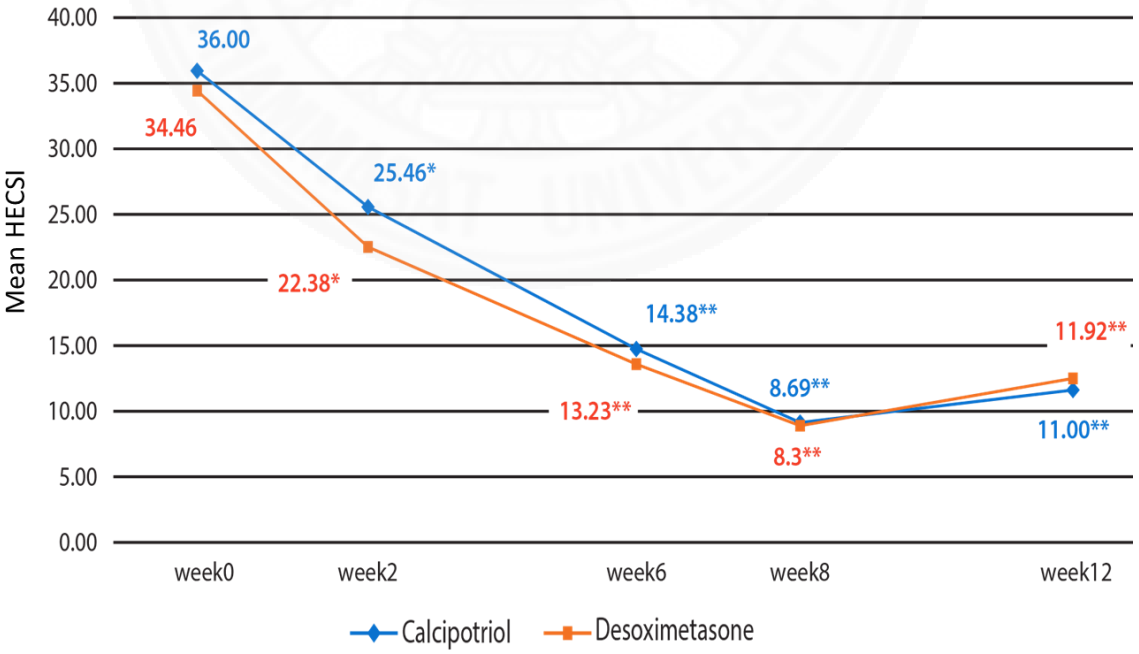
4.2.1 Objective assessment

The Objective assessment of clinical severity was evaluated by the same investigator at baseline before starting the experiment, then at every visit during the treatment period (2nd, 6th and 8th week respectively) using the hand eczema severity index (HECSI). At baseline, the HECSI between the two regimens was compared to demonstrate whether there is any different of clinical severity between the two groups before started the treatment. The result found that the HECSI scores at baseline in calcipotriol-treated group was 36.00 ± 13.54 and 34.46 ± 14.22 in desoximetasone-treated group with no statistical difference in HECSI between the two regimens ($P>0.05$). The overall result displayed by the end of treatment period showed an improvement of HECSI in both calcipotriol and desoximetasone - treated sides.

In calcipotriol-treated group, mean HECSI was found significantly improved compared with the score at baseline ($P=0.002$) since the second week after treatment with an approximately 30% reduction of the score was found. After continue

treatment, mean HECSI became even more decreased compared with the baseline in every follow up. Around 60% reduction of mean HECSI from the baseline was found at the 6th week of treatment period and the score also demonstrate statistically significant decrease (P=0.001) when compared to the baseline. By the end of the treatment period, at the 8th week, mean HECSI was show statistically improvement (p = 0.001) and reached its maximum reduction with approximately 76% decrease from the baseline. (Figure 4.2) (Table 4.4 – 4.5).

Participants treated with desoximetasone were also accomplish the improvement in clinical severity similar to calcipotriol-treated side. Mean HECSI of desoximetasone group started to decrease significantly correlated with the baseline since the second week after treatment (p = 0.002) with approximately 35% reduction of the score. Then after continuing the treatment, the mean score was consistently significantly decrease in every visit. The mean HECSI of desoximetasone group was 13.23 ± 8.03 at the 6th week with around 61% reduction from the baseline and by the end of treatment period (the 8th week), the mean scores were demonstrated about 76% reduction from baseline with statistically significant (p = 0.001). (Figure 4.2) (Table 4.4 – 4.5).



P value of intra-group comparison: * P = 0.002 ** P = 0.001

Figure 4.2 Mean HECSI at each visit

Moreover, when compared mean HECSI scores between calcipotriol and desoximetasone-treated side, there was no statistically significant difference in any visit until the end of treatment period.

After discontinuing the treatment, all the patients were treated with only petrolatum ointment on both hands for 4 weeks and were assessed the severity of their hands again for any relapse. At the end of this follow up period, mean HECSI was significantly increased in both regimens correlated with the score from the last visit of treatment period. Calcipotriol-treated side showed less increase of mean HECSI ($p < 0.05$) than desoximetasone-treated side ($p < 0.01$). The score displayed approximately 27% rising form the lastest score at the end of treatment period while the increment of the score in desoximetasone group demonstrate about 44%. (Table 10). Although mean HECSI of both regimens was significantly increased compared to the lastet score at the end of treatment period, when compared mean HECSI of the follow up period to the baseline scores, there was still a statistical significant improvement of the clinical severity (P=0.001). The mean HECSI was lower than baseline approximately 70% in both treated side and there was no statistically significant difference of the score at the end of follow-up period. (Table 4.4).

Table 4.4 Intra – group comparison of mean HECSI

Groups		**Difference from baseline to each visit**			
		BL-2th week	**BL-6th week**	**BL-8th week**	**BL-12th week**
Calcipotriol	Mean ± SD	10.36±7.58	21.62±7.77	27.31±7.88	25±8.42
	% reduction	29.20%	60.05%	75.91%	68.08%
	p value	0.002	0.001	0.001	0.001
Desoximetasone	Mean ± SD	12.08±9.24	21.23±11.79	26.16±13.88	22.54±13.31
	% reduction	35.05%	61.61%	75.86%	66.89%
	p value	0.002	0.001	0.001	0.001
Calcipotriol vs Desoximetasone (*p* value)		0.36	0.75	0.54	0.22

Table 4.5 Inter - group comparison of mean HECSI

Groups		Treatment				Follow-up
		Baseline	**BL-2nd week**	**BL-6th week**	**BL-8th week**	
Calcipotriol	Mean ± SD	36.00 ± 13.54	25.46 ± 11.47	14.38 ± 8.10	8.69 ± 5.28	11.00 ± 5.90
Desoximetasone	Mean ± SD	34.46 ± 14.22	22.38 ± 8.91	13.23 ± 8.03	8.30 ± 4.36	11.92 ± 6.07
***p* value**		0.84	0.39	0.76	0.92	0.76

Table 4.6 Inter and intra - group comparison of mean HECSI at 8th -12th week

Group		Difference of mean HECSI 8th -12th week
Calcipotriol	**% increase**	26.6%
	p value	0.049*
Desoximetasone	**% increase**	43.6%
	p value	0.002*
Calcipotriol vs Desoximetasone (p value)		0.102

*p<0.05, **p<0.01

4.2.2 Subjective assessment

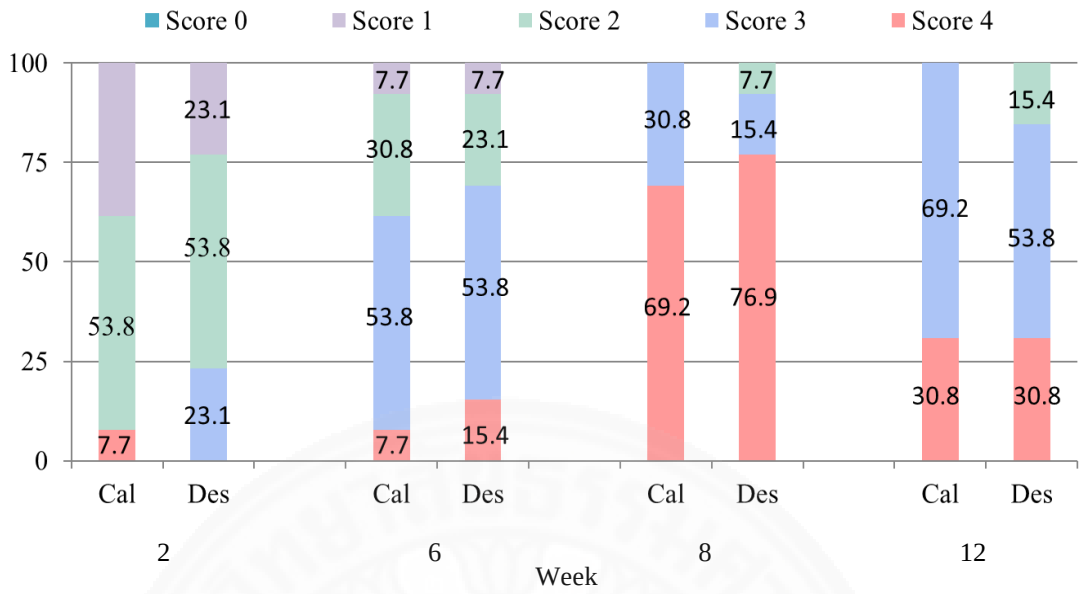
Apart from the objective assessment evaluated by researcher, participants were also evaluated the severity of their own hands by using quartile grading scale (QGS) which is a subjective assessment in this study. The result demonstrated some improvement since the second week of treatment in both regimens. According to the result, all of participants treated with calcipotriol experienced some improvement after only two weeks of medical application. Almost 8% of the participants showed more than 75% improvement. Meanwhile, the result of desoximetasone group also showed some improvement within the first two week after

treatment. However, there was no participants in desoximetasone - treated side showed more than 75% improvement. The percent improvement assessed by the patients was still consistently increase all the way toward the end of treatment in both groups. All the participant treated with calcipotriol achieved more than 50% of clinical improvement by the end of the treatment period compared with 92% of the participants treated with desoximetasone. The majority of patients in Calcipotriol - treated side experienced a highly clinical improvement with around 70%. Likewise, most of the patients treated with desoximetasone were also demonstrated a highly clinical improvement with almost 77%. (Table 4.7) (Figure 4.3)

At the twelfth week, all patients evaluated the severity of their hands again for any relapse. All participants treated with calcipotriol still estimate more than 50% of clinical improvement with almost 32% percent of the participants were having more than 75% of clinical improvement. Meanwhile, not every participant in desoximetasone group rate more than 50% improvement. Only 85% of the subjects treated with desoximetasone achieved more than 50% improvement with around 15% of the participants addressed less than 50% improvement. However, the percentage of improvement was not significant difference between both regimens in any visits ($p > 0.05$). (Table 4.7)

Table 4.7 Participants' self-assessment

Degree of improvement	**No improvement**	**1-25%**	**26-50%**	**51-75%**	**76-100%**	***p* values**
Week 2						
Calcipotriol	0	38.5	53.8	0	7.7	0.41
Desoximetasone	0	23.1	53.8	23.1	0	
Week 6						
Calcipotriol	0	7.7	30.8	53.8	7.7	0.45
Desoximetasone	0	7.7	23.1	53.8	15.4	
Week 8						
Calcipotriol	0	0	0	30.8	69.2	0.26
Desoximetasone	0	0	7.7	15.4	76.9	
Week 12						
Calcipotriol	0	0	0	69.2	30.8	0.74
Desoximetasone	0	0	15.4	53.8	30.8	



Score 0 = no improvement, score 1 = 1-25% improvement, score 2 = 26-50% improvement, score 3 = 51-75% improvement, score 4 = 75-100% improvement.

Figure 4.3 Participants' self-assessment

4.3 Adverse effects

Only local side effect was detected in this study. Scaling was the most common side effect from Calcipotriol - treated side which exhibited in all of participants during a few weeks after medical application. Around 72% of cases developed only mild scaling which spontaneously resolved during the sixed and eighth week of treatment. Mild dryness was the second most common local side effect in calcipotriol group that involve about 15.38% of the participants. Another local side effect in patients treated with calcipotriol was moderate crackle which involved around 7.7% of the patients. These symptoms were also gradually spontaneous resolved within the sixed and eighth week of treatment period along with the cessation of localize scaling.

Table 4.8 Adverse effects

Side effects	Calipotriol		Desoxymethasone	
	N	**%**	**N**	**%**
Mid scaling	10	76.92	0	0.00
Moderate scaling	3	23.08	0	0.00
Mid dryness	1	7.69	10	76.92
Moderate dryness	1	7.69	0	0.00
Mid stinging	1	7.69	4	30.77
Mid crackle	0	0.00	2	15.38
Moderated crackle	1	7.69	0	0.00
Mid erythema	0	0.00	2	15.38

For desoximetasone - treated side, the most common side effect was mild dryness which occurred almost 77% of participants followed by stinging sensation that exhibit about 31% of patients. The stinging and dryness sensation developed during the first week after treatment and continually exhibited until the end of treatment period. However, the symptoms were gradually subsided during placebo period after applying petrolatum ointment and was resolved within a few days. Others side effects including crackle and erythema were found in 15% of participants treated with desoximetasone. Likewise, these symptoms were also gradually improved and resolved after applying petrolatum ointment and discontinue desoximetasone. In addition, other serious side effects such as skin atrophy and telangiectasia that can be found followed chronic usage of topical steroid were not detected in this study. (Table4.4.8).

4.4 Discussion

Chronic hand eczema is a common dermatologic condition which frequently relapses and has a substantial health economic, socio-medical impact on individuals. Most cases of hand eczema have multifactorial etiologies thus these make the management complex. Topical use of corticosteroids alone or in combination with keratolytic agents, retinoic acid and emollients, is the treatment of choice. However, these treatments often have an unsatisfactory result and are prone to induce side effects.

Topical vitamin D derivative was approved and has been liberally used in the treatment of adult plaque type psoriasis. Moreover, it was reported to have a profitable efficacy in the treatment of many inflammatory diseases other than psoriasis which have the same pathogenic characters of impaired keratinocyte differentiation and proliferation (8, 9). Previous study demonstrated that twice daily application of topical vitamin D analogues had an excellent therapeutic effect in a clinical cases reported of 5 patients with hyperkeratotic palmoplantar eczema (11). In four patients, the lesions almost disappeared after 2 to 8 weeks of application and one patient found highly improvement after 7 weeks of treatment. The result showed no adverse reaction and when relapses occurred, the patients responded well to treatment (11). Another study (12) reported the successful treatment of refractory CHE with calcipotriol in combination with betamethasone ointment. The study demonstrated 2 patients whose lesions were completely cured and one patient showed 90% improvement after the treatment in 5-24 weeks. From what mentioned above can be assumed that topical vitamin D derivative may have the potential to be an alternative treatment for CHE and therefore, needs further studies to give a stronger statistical evidence.

This study is the first randomized double-blind, controlled trial which compared the efficacy of topical vitamin D analogue with one of the first-line therapy for hand eczema, a topical corticosteroid, in the treatment of patients with CHE. The study compared the efficacy of 0.005% calcipotriol ointment with 0.25% desoximetasone ointment during 8-week of treatment period. Patch testing was initially underwent in all subjects to exclude any possibility of contact hypersensitivity. After that all the participants who were negative for patch test were assessed the clinical severity by using HECSI (The hand eczema severity index) and digital photographs during the treatment period and also follow-up period. Moreover, patients in our study can also evaluated the severity of their own hand by using Quartile grading score in every visit which can determined the clinical significant. After discontinuing the topical medications, patients were prescribed only petrolatum ointment to apply over both of their hands for 4 weeks and relapse was evaluated at the end of this follow-up period by the same assessment methods. Skin protection program such as avoidance of any suspected irritant/allergen and hand care was also provide to all the participants through the study period.

The result in this study reveal that both calcipotriol and desoximetasone ointment show similar efficacious therapeutic effect in the treatment of chronic hand eczema. The reduction of mean HECSI in calcipotriol - treated side compared with desoximetasone - treated side demonstrated no statistical difference ($P>0.05$) in any visit and also at the end of the treatment period. However, both treated groups yielded marked statistically significant reduction of mean HECSI from the pre-treatment score within their group ($P<0.01$) with very few side effects. Mean HECSI in calcipotriol – treated group was statistically improved compared with baseline since the second week of treatment ($P = 0.002$) and consistently even more different in every visit until the end of the treatment period ($P = 0.001$). Likewise, mean HECSI in desoximetasone - treated side was also statistically improved compared with baseline since the second week of treatment ($P = 0.002$) and continually more different in every visit until the end of treatment ($P=0.001$). The maximum reduction of mean HECSI was up to almost 76% in both regimens after 8 weeks of treatment.

Four weeks after the last treatment (12^{th} week), all patients were evaluated again for any relapse. Mean HECSI at 8^{th} week was compared with the HECSI at 12^{th} week within each treatment to evaluated any difference in severity score after discontinuing the treatment. The result show a statistically significant increase of mean HECSI within both calcipotriol and desoximetasone - treated side when compared to the latest treatment ($P<0.05$). This mean that after discontinuing the treatment, the symptom tends to exhibit more severe than the last time patients were treated. Although, recurrences were noticed following both treatments, it seems that higher rate of relapses was found in desoximetasone group more than calcipotriol group. The increment of mean HECSI at the end of follow-up period in calcipotriol-treated side was around 26.5% while the increase rate of desoximetasone was around 43.6%. This may be the consequence of tachyphylaxis from prolonged use of topical corticosteroids. Nevertheless, the clinical presentation at the end of follow up period was not as severe as pre-treatment period. The mean HECSI at 12th week of both treatments sides were less than baseline around 70% and were significantly improved when compared with the score at the baseline ($P<0.01$).

Moreover, in term of subjective assessment, there was no significant differences of clinical improvement from patients' perspectives between the two

treated-regimens. The result showed that all participants reported at least 50% improvement of the clinical severity in calcipotriol group by the end of treatment compared to 92% in desoximetasone group and after 4 weeks of follow-up period, the clinical severity in all participants treated with calcipotriol still present more than 50% improvement while there was only 84.6% of participants treated with desoximetasone demonstrated more than 50% improvement of clinical severity. However, when we compared the outcome between the two treatments, there was no statistical difference in any visit during the treatment period and also at the end of follow-up period. This can indicate that in term of patients' opinion, both treatment regimens provide the similar beneficial therapeutic result during the treatment period and also after discontinuing the medication.

From what mentioned above, calcipotriol yielded an excellent therapeutic result in the treatment of CHE especially for hyperkeratotic type which is the most common clinical variant in our study. The outcome was similar to the former study by Egawa et al. (11), which also demonstrated a distinguish effect of calcipotriol in hyperkeratotic palmoplantar eczema. What make this study different from the previous one is that, this study was the first experiment to use both standard objective and subjective assessment methods in the evaluation of clinical severity and also compare the outcome with the standard treatment of CHE. Moreover, this study demonstrated the efficacy of calcipotriol ointment alone unlike the previous study by Yang et al. that show the efficacy of the combination medicine (Calcipotriol 50 microgram/g. Betamethasone 500 microgram/g)

Concerning of the side effect, there was no serious side effect or any systemic side effect was found in this study. Skin atrophy, telangiectasia or any discoloration of the skin which are the serious adverse reaction from chronic application of corticosteroid or even other contact reaction such as acneiform eruption from accidentally touching other part of the body especially the face was also not reported in this study. There were a few localize side effects detected in both treatment group. Scaling was commonly reported in calcipotriol treated group and was continually decrease or spontaneously resolved during the treatment period. This reaction may be explained by the result of the modulated keratinocyte differentiation and stimulated terminal differentiation effect which are the main mechanism of vitamin D derivative

(5, 84) . The most common side effect in participants treated with desoximetasone was skin dryness which can probably be the consequence from chronic corticosteroid application. Topical potent corticosteroids have an anti-inflamatory and immunosuppressive properties thus, it promotes clinical improvement in CHE. However, topical corticosteroids can also interfere epidermal barrier homeostasis, stratum corneum integrity, cohesion (85) and further reduce lipid synthesis; therefore, that is why dryness and stinging sensation were the common side effect in participants treated with desoximetasone. Nevertheless, these reactions were resolved after discontinue medication and after applying emollient. Hence, application of topical emollient was suggested to reduce and solve this adverse reaction.

The limitation of our study included small number of participants and short period of the follow-up time to determine relapses. In addition, participants seem to lost compliance at the beginning because of their working times. However, by improved doctor-patient relationship and provide an adequate information about the treatment, the participants appear to be more cooperate and have a better adherence.

CHAPTER 5
CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusion

The management of chronic hand eczema is complex and requires various treatment strategies. Topical use of corticosteroids is the treatment of choice for CHE however, long-term application often have an unsatisfactory result and are prone to induce side effects. A twice daily application of topical vitamin D analogues has been reported to have an excellent therapeutic effect on chronic hyperkeratotic hand eczema (11, 12). Therefore, this former study is an inspiration to conduct further studies with a larger number of participants and more standardized assessment methods in term to yield a better precision and accuracy.

This research is the randomized double-blinded, controlled study to evaluate the efficacy and safety of calcipotriol ointment alone in the treatment of CHE. The study compared the efficacy of calcipotriol ointment with a potent topical corticosteroid, the first line treatment of CHE by using both standard objective and subjective assessment tools which make it different from the others former studies (11, 12). The results revealed that calcipotriol ointment demonstrate similar excellent therapeutic efficacy as desoximetasone ointment in the treatment of CHE. This topical vitamin D analogue yield marked statistically significant improvement of clinical severity in term of the reduction in mean HECSI from the baseline ($P<0.001$) and also by patient self-assessment without any different when compared with the desoximetasone treated group. Therefore, all mentioned above can imply that both investigator's evaluation and from patients' perspective, calcipotriol ointment may have the potential to be an alternative treatment option for CHE exclusively in hyperkeratotic variant which is the most clinical characteristic found in this study.

The recurrences were noticed following both medications after terminated the treatment. However, the clinical assessment score was still significantly less than the score at baseline. All the participants demonstrated more than 50% improvement regarding to patient self-assessment and around 70% reduction of mean HECSI was revealed at the end of follow-up period. The relapse seems to have a higher rate in

desoximetasone-treated group more than calcipotriol-treated group which may be explained by the tachyphylaxis from prolonged use of topical corticosteroids.

Regarding to the safety, there was no serious reaction or any systemic side effect found during the study. The serious adverse reaction from chronic application of corticosteroid were also not reported in this study. Both calcipotriol and desoximetasone ointment exhibit only mild localize adverse reactions. Scaling was the most frequently side effect found in calcipotriol group while dryness and stinging sensation were commonly found in desoximetasone group. However, these reactions were spontaneous resolve or gradually resolution after application of emollient.

In conclusion, topical calcipotriol seems to offer an effective and safe alternative form of treatment for CHE especially in hyperkeratotic type. The significant improvement of clinical severity can be seen since the second week of application and further improvement up to 75% by 8 weeks of treatment with only minimal localized side effect. It is a steroid-sparing treatment option which can be useful for long-term treatment to avoid serious adverse reaction from chronic application and also avoid any contact reaction of topical potent corticosteroid. Finally, as regard to patients' perspective, calcipotriol ointment yield a satisfactory therapeutic efficacy in the treatment of chronic hand eczema.

5.2 Recommendations

5.2.1 Recommendation for clinical application

5.2.1.1 Our study recommends that for patient with CHE especially in hyperkeratotic type, calcipotriol can be considered as another non-steroidal alternative treatment option.

5.2.1.2 Any emollient is also recommended along with the treatment to help diminishing scaling or dryness and promote a better result.

5.2.2 Recommendation for further study

5.2.2.1 Further studies with a larger number of participants may provide the better precision and accuracy

5.2.2.2 Further studies with longer duration of follow up will help us determine better tendency of the relapse rate.

REFERENCES

1. Hald M, Berg ND, Elberling J, Johansen JD. Medical consultations in relation to severity of hand eczema in the general population. Br J Dermatol. 2008;158(4):773-7.

2. Dibenedetti D, Baranowski E, Zelt S, Reynolds M, Sherrill B. Assessing United States Patient and Dermatologist Experiences with Severe Chronic Hand Eczema. J Clin Aesthet Dermatol. 2015;8(11):19-27.

3. Diepgen TL, Andersen KE, Chosidow O, Coenraads PJ, Elsner P, English J, et al. Guidelines for diagnosis, prevention and treatment of hand eczema--short version. J Dtsch Dermatol Ges. 2015;13(1):77-85.

4. English J, Aldridge R, Gawkrodger DJ, Kownacki S, Statham B, White JM, et al. Consensus statement on the management of chronic hand eczema. Clin Exp Dermatol. 2009;34(7):761-9.

5. de Kerkhof PCMv. In vivo effects of vitamin D3 analogues. Journal of Dermatological Treatment. 1998;9(sup3):S25-S9.

6. Bagot M, Charue D, Lescs MC, Pamphile RP, Revuz J. Immunosuppressive effects of 1,25-dihydroxyvitamin D3 and its analogue calcipotriol on epidermal cells. Br J Dermatol. 1994;130(4):424-31.

7. Rostkowska-Nadolska B, Sliupkas-Dyrda E, Potyka J, Kusmierz D, Fraczek M, Krecicki T, et al. Vitamin D derivatives: calcitriol and tacalcitol inhibits interleukin-6 and interleukin-8 expression in human nasal polyp fibroblast cultures. Adv Med Sci. 2010;55(1):86-92.

8. Holm EA, Jemec GB. The therapeutic potential of calcipotriol in diseases other than psoriasis. Int J Dermatol. 2002;41(1):38-43.

9. Wat H, Dytoc M. Off-label uses of topical vitamin D in dermatology: a systematic review. J Cutan Med Surg. 2014;18(2):91-108.

10. Braun GS, Witt M, Mayer V, Schmid H. Hypercalcemia caused by vitamin D3 analogs in psoriasis treatment. Int J Dermatol. 2007;46(12):1315-7.

11. Egawa K. Topical vitamin D3 derivatives in treating hyperkeratotic palmoplantar eczema: a report of five patients. J Dermatol. 2005;32(5):381-6.

12. Yang M, Chang JM. Successful treatment of refractory chronic hand eczema with calcipotriol/betamethasone ointment: A report of three cases. Exp Ther Med. 2015;10(5):1943-6.

13. Menne T, Johansen JD, Sommerlund M, Veien NK, Danish Contact Dermatitis G. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. Contact Dermatitis. 2011;65(1):3-12.

14. Diepgen TL, Purwins S, Posthumus J, Kuessner D, John SM, Augustin M. Cost-of-illness analysis of patients with chronic hand eczema in routine care in Germany: focus on the impact of occupational disease. Acta Derm Venereol. 2013;93(5):538-43.

15. Diepgen TL, Elsner P, Schliemann S, Fartasch M, Kollner A, Skudlik C, et al. Guideline on the management of hand eczema ICD-10 Code: L20. L23. L24. L25. L30. J Dtsch Dermatol Ges. 2009;7 Suppl 3:S1-16.

16. Apfelbacher C, Molin S, Weisshaar E, Bauer A, Elsner P, Mahler V, et al. Characteristics and provision of care in patients with chronic hand eczema: updated data from the CARPE registry. Acta Derm Venereol. 2014;94(2):163-7.

17. Meding B. Epidemiology of hand eczema in an industrial city. Acta Derm Venereol Suppl (Stockh). 1990;153:1-43.

18. Meding B, Jarvholm B. Hand eczema in Swedish adults - changes in prevalence between 1983 and 1996. J Invest Dermatol. 2002;118(4):719-23.

19. Thyssen JP, Johansen JD, Linneberg A, Menne T. The epidemiology of hand eczema in the general population--prevalence and main findings. Contact Dermatitis. 2010;62(2):75-87.

20. Dotterud LK, Smith-Sivertsen T. Allergic contact sensitization in the general adult population: a population-based study from Northern Norway. Contact Dermatitis. 2007;56(1):10-5.

21. Mortz CG, Bindslev-Jensen C, Andersen KE. Hand eczema in The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS): prevalence, incidence and risk factors from adolescence to adulthood. Br J Dermatol. 2014;171(2):313-23.

22. Johannisson A, Ponten A, Svensson A. Prevalence, incidence and predictive factors for hand eczema in young adults - a follow-up study. BMC Dermatol. 2013;13:14.

23. Molin S, Diepgen TL, Ruzicka T, Prinz JC. Diagnosing chronic hand eczema by an algorithm: a tool for classification in clinical practice. Clin Exp Dermatol. 2011;36(6):595-601.

24. Dickel H, Kuss O, Schmidt A, Kretz J, Diepgen TL. Importance of irritant contact dermatitis in occupational skin disease. Am J Clin Dermatol. 2002;3(4):283-9.

25. Ibler KS, Jemec GB, Garvey LH, Agner T. Prevalence of delayed-type and immediate-type hypersensitivity in healthcare workers with hand eczema. Contact Dermatitis. 2016.

26. Schwensen JF, Friis UF, Menne T, Johansen JD. One thousand cases of severe occupational contact dermatitis. Contact Dermatitis. 2013;68(5):259-68.

27. Amaro C, Goossens A. Immunological occupational contact urticaria and contact dermatitis from proteins: a review. Contact Dermatitis. 2008;58(2):67-75.

28. Levin C, Warshaw E. Protein contact dermatitis: allergens, pathogenesis, and management. Dermatitis. 2008;19(5):241-51.

29. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006;38(4):441-6.

30. Thyssen JP, Linneberg A, Ross-Hansen K, Carlsen BC, Meldgaard M, Szecsi PB, et al. Filaggrin mutations are strongly associated with contact sensitization in individuals with dermatitis. Contact Dermatitis. 2013;68(5):273-6.

31. de Jongh CM, Khrenova L, Verberk MM, Calkoen F, van Dijk FJ, Voss H, et al. Loss-of-function polymorphisms in the filaggrin gene are associated with an increased susceptibility to chronic irritant contact dermatitis: a case-control study. Br J Dermatol. 2008;159(3):621-7.

32. Johansen JD, Hald M, Andersen BL, Laurberg G, Danielsen A, Avnstorp C, et al. Classification of hand eczema: clinical and aetiological types. Based on the guideline of the Danish Contact Dermatitis Group. Contact Dermatitis. 2011;65(1):13-21.

33. Schuttelaar ML, Coenraads PJ, Huizinga J, De Monchy JG, Vermeulen KM. Increase in vesicular hand eczema after house dust mite inhalation provocation: a double-blind, placebo-controlled, cross-over study. Contact Dermatitis. 2013;68(2):76-85.

34. Duman N, Uzunali E. Clinical assessment of the severity of chronic hand eczema: correlations between six assessment methods. The European Research Journal. 2015;1(2):44-9.

35. Kutting B, Baumeister T, Weistenhofer W, Pfahlberg A, Uter W, Drexler H. Effectiveness of skin protection measures in prevention of occupational hand eczema: results of a prospective randomized controlled trial over a follow-up period of 1 year. Br J Dermatol. 2010;162(2):362-70.

36. Held E, Skoet R, Johansen JD, Agner T. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. Br J Dermatol. 2005;152(2):302-7.

37. Ruzicka T, Lynde CW, Jemec GB, Diepgen T, Berth-Jones J, Coenraads PJ, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. Br J Dermatol. 2008;158(4):808-17.

38. Nilay Duman EU. Clinical assessment of the severity of chronic hand eczema: correlations between six assessment methods. The European Research Journal. 2015;1(2):44-9.

39. Skudlik C, Dulon M, Pohrt U, Appl KC, John SM, Nienhaus A. Osnabrueck hand eczema severity index--a study of the interobserver reliability of a scoring system assessing skin diseases of the hands. Contact Dermatitis. 2006;55(1):42-7.

40. Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol. 2008;159(5):997-1035.

41. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-6.

42. Coenraads PJ, Van Der Walle H, Thestrup-Pedersen K, Ruzicka T, Dreno B, De La Loge C, et al. Construction and validation of a photographic guide for assessing severity of chronic hand dermatitis. Br J Dermatol. 2005;152(2):296-301.

43. Hald M, Veien NK, Laurberg G, Johansen JD. Severity of hand eczema assessed by patients and dermatologist using a photographic guide. Br J Dermatol. 2007;156(1):77-80.

44. Agner T, Jungersted JM, Coenraads PJ, Diepgen T. Comparison of four methods for assessment of severity of hand eczema. Contact Dermatitis. 2013;69(2):107-11.

45. Kraft JN, Lynde CW. Moisturizers: what they are and a practical approach to product selection. Skin Therapy Lett. 2005;10(5):1-8.

46. Held E, Lund H, Agner T. Effect of different moisturizers on SLS-irritated human skin. Contact Dermatitis. 2001;44(4):229-34.

47. Ramsing DW, Agner T. Preventive and therapeutic effects of a moisturizer. An experimental study of human skin. Acta Derm Venereol. 1997;77(5):335-7.

48. Zachariae C, Held E, Johansen JD, Menne T, Agner T. Effect of a moisturizer on skin susceptibility to NiCl2. Acta Derm Venereol. 2003;83(2):93-7.

49. Moller H, Svartholm H, Dahl G. Intermittent maintenance therapy in chronic hand eczema with clobetasol propionate and flupredniden acetate. Curr Med Res Opin. 1983;8(9):640-4.

50. Kao JS, Fluhr JW, Man M-Q, Fowler AJ, Hachem J-P, Crumrine D, et al. Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: inhibition of epidermal lipid synthesis accounts for functional abnormalities. Journal of Investigative Dermatology. 2003;120(3):456-64.

51. Loden M, Wiren K, Smerud KT, Meland N, Honnas H, Mork G, et al. The effect of a corticosteroid cream and a barrier-strengthening moisturizer in hand eczema. A double-blind, randomized, prospective, parallel group clinical trial. J Eur Acad Dermatol Venereol. 2012;26(5):597-601.

52. Veien NK, Olholm Larsen P, Thestrup-Pedersen K, Schou G. Long-term, intermittent treatment of chronic hand eczema with mometasone furoate. Br J Dermatol. 1999;140(5):882-6.

53. Schnopp C, Remling R, Mohrenschlager M, Weigl L, Ring J, Abeck D. Topical tacrolimus (FK506) and mometasone furoate in treatment of dyshidrotic palmar eczema: a randomized, observer-blinded trial. J Am Acad Dermatol. 2002;46(1):73-7.

54. Belsito DV, Fowler JF, Jr., Marks JG, Jr., Pariser DM, Hanifin J, Duarte IA, et al. Pimecrolimus cream 1%: a potential new treatment for chronic hand dermatitis. Cutis. 2004;73(1):31-8.

55. Hordinsky M, Fleischer A, Rivers JK, Poulin Y, Belsito D, Hultsch T. Efficacy and safety of pimecrolimus cream 1% in mild-to-moderate chronic hand dermatitis: a randomized, double-blind trial. Dermatology. 2010;221(1):71-7.

56. Paller AS, Lebwohl M, Fleischer AB, Jr., Antaya R, Langley RG, Kirsner RS, et al. Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: results from 3 randomized, comparative studies. J Am Acad Dermatol. 2005;52(5):810-22.

57. Katsarou A, Makris M, Papagiannaki K, Lagogianni E, Tagka A, Kalogeromitros D. Tacrolimus 0.1% vs mometasone furoate topical treatment in allergic contact hand eczema: a prospective randomized clinical study. Eur J Dermatol. 2012;22(2):192-6.

58. Hanifin JM, Stevens V, Sheth P, Breneman D. Novel treatment of chronic severe hand dermatitis with bexarotene gel. Br J Dermatol. 2004;150(3):545-53.

59. Pion IA, Koenig KL, Lim HW. Is dermatologic usage of coal tar carcinogenic? A review of the literature. Dermatol Surg. 1995;21(3):227-31.

60. Roelofzen JH, Aben KK, van der Valk PG, van Houtum JL, van de Kerkhof PC, Kiemeney LA. Coal tar in dermatology. J Dermatolog Treat. 2007;18(6):329-34.

61. Bissonnette R, Diepgen TL, Elsner P, English J, Graham-Brown R, Homey B, et al. Redefining treatment options in chronic hand eczema (CHE). J Eur Acad Dermatol Venereol. 2010;24 Suppl 3:1-20.

62. León FJd, Berbegal L, Silvestre JF. Management of Chronic Hand Eczema. Actas Dermosifiliogr. 2015;106:533-44.

63. Lynde C, Guenther L, Diepgen TL, Sasseville D, Poulin Y, Gulliver W, et al. Canadian hand dermatitis management guidelines. J Cutan Med Surg. 2010;14(6):267-84.

64. Ruzicka T, Larsen FG, Galewicz D, Horvath A, Coenraads PJ, Thestrup-Pedersen K, et al. Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of a randomized, double-blind, placebo-controlled, multicenter trial. Arch Dermatol. 2004;140(12):1453-9.

65. Bissonnette R, Worm M, Gerlach B, Guenther L, Cambazard F, Ruzicka T, et al. Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. Br J Dermatol. 2010;162(2):420-6.

66. Paulden M, Rodgers M, Griffin S, Slack R, Duffy S, Ingram JR, et al. Alitretinoin for the treatment of severe chronic hand eczema. Health Technol Assess. 2010;14 Suppl 1:39-46.

67. Thestrup-Pedersen K, Andersen KE, Menne T, Veien NK. Treatment of hyperkeratotic dermatitis of the palms (eczema keratoticum) with oral acitretin. A single-blind placebo-controlled study. Acta Derm Venereol. 2001;81(5):353-5.

68. Granlund H, Erkko P, Eriksson E, Reitamo S. Comparison of cyclosporine and topical betamethasone-17,21-dipropionate in the treatment of severe chronic hand eczema. Acta Derm Venereol. 1996;76(5):371-6.

69. Egan CA, Rallis TM, Meadows KP, Krueger GG. Low-dose oral methotrexate treatment for recalcitrant palmoplantar pompholyx. J Am Acad Dermatol. 1999;40(4):612-4.

70. Grundmann-Kollmann M, Behrens S, Peter RU, Kerscher M. Treatment of severe recalcitrant dermatoses of the palms and soles with PUVA-bath versus PUVA-cream therapy. Photodermatol Photoimmunol Photomed. 1999;15(2):87-9.

71. Sezer E, Etikan I. Local narrowband UVB phototherapy vs. local PUVA in the treatment of chronic hand eczema. Photodermatol Photoimmunol Photomed. 2007;23(1):10-4.

72. Rosen K, Mobacken H, Swanbeck G. Chronic eczematous dermatitis of the hands: a comparison of PUVA and UVB treatment. Acta Derm Venereol. 1987;67(1):48-54.

73. Sieg A, Wascotte V. Diagnostic and therapeutic applications of iontophoresis. J Drug Target. 2009;17(9):690-700.

74. Guillet MH, Wierzbicka E, Guillet S, Dagregorio G, Guillet G. A 3-year causative study of pompholyx in 120 patients. Arch Dermatol. 2007;143(12):1504-8.

75. Wollina U, Uhlemann C, Elstermann D, Kober L, Barta U. [Therapy of hyperhidrosis with tap water iontophoresis. Positive effect on healing time and lack of recurrence in hand-foot eczema]. Hautarzt. 1998;49(2):109-13.

76. Brown T. Strategies for prevention: occupational contact dermatitis. Occup Med (Lond). 2004;54(7):450-7.

77. Held E, Mygind K, Wolff C, Gyntelberg F, Agner T. Prevention of work related skin problems: an intervention study in wet work employees. Occup Environ Med. 2002;59(8):556-61.

78. Agner T, Held E. Skin protection programmes. Contact Dermatitis. 2002;47(5):253-6.

79. Ibler KS, Jemec GB, Diepgen TL, Gluud C, Lindschou Hansen J, Winkel P, et al. Skin care education and individual counselling versus treatment as usual in healthcare workers with hand eczema: randomised clinical trial. BMJ. 2012;345:e7822.

80. Skudlik C, Wulfhorst B, Gediga G, Bock M, Allmers H, John SM. Tertiary individual prevention of occupational skin diseases: a decade's experience with recalcitrant occupational dermatitis. Int Arch Occup Environ Health. 2008;81(8):1059-64.

81. Bury Y, Ruf D, Hansen CM, Kissmeyer AM, Binderup L, Carlberg C. Molecular evaluation of vitamin D3 receptor agonists designed for topical treatment of skin diseases. J Invest Dermatol. 2001;116(5):785-92.

82. Fogh K, Kragballe K. Vitamin D3 analogues. Clin Dermatol. 1997;15(5):705-13.

83. Nieboer C, Verburgh CA. Psoriasis treatment with vitamin D3 analogue MC 903. Br J Dermatol. 1992;126(3):302-3.

84. Brautigam M, Hubner H, Rach P, Thieroff-Ekerdt R. Effects of calcipotriol (MC 903) and calcitriol after topical application on the skin of hairless rats. Much lower effect of calcipotriol on systemic calcium homeostasis. Skin Pharmacol. 1992;5(2):87-92.

85. Kao JS, Fluhr JW, Man MQ, Fowler AJ, Hachem JP, Crumrine D, et al. Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and

stratum corneum integrity: inhibition of epidermal lipid synthesis accounts for functional abnormalities. J Invest Dermatol. 2003;120(3):456-64.

APPENDIX

APPENDIX

CASE RECORD FORM

WK	วันที่	NO.	HN

แบบฟอร์มข้อมูล (Case record form) สำหรับผู้เข้าร่วมการวิจัย

☐ โรงพยาบาลธรรมศาสตร์ ☐ โรงพยาบาลยาสูบ

- ชื่อ-สกุล . . . . . .
- เพศ ☐ ชาย ☐ หญิง อายุ . . . . . ปี
- เบอร์โทรศัพท์ . . . . . .
- เบอร์โทรศัพท์บุคคลใกล้ชิด (โปรดระบุ). . . . . .
- อาชีพ
  - ☐ บุคลากรทางด้านสาธารณสุข (โปรดระบุ เช่น แพทย์ พยาบาล ผู้ช่วยพยาบาล ฯลฯ). . . . . .
  - ☐ ช่างทำผม/พนักงานร้านเสริมสวย
  - ☐ ประกอบอาชีพเกี่ยวกับอาหาร (โปรดระบุ เช่น แม่ครัว คนทำขนม พนักงานล้างจาน ฯลฯ) . . . . . .
  - ☐ พนักงานทำความสะอาด
  - ☐ พนักงานห้องแล็ปฯ/พนักงานโรงงานอุตสาหกรรม (โปรดระบุ เช่น โรงงานประกอบชิ้นส่วนอิเล็กทรอนิกส์ โรงเชื่อม/กลึง/หลอมโลหะ โรงงานผลิตสารเคมี ฯลฯ). . . . . .
  - ☐ พนักงานก่อสร้าง/ช่างทาสี/ช่างไม้/ช่างปั้น / แกะสลัก
  - ☐ อาชีพอื่นๆ (โปรดระบุ) . . . . . .
- ระยะเวลาทำงาน . . . . . ชั่วโมง/วัน
- ท่านทำอาชีพนี้มานาน . . . . . ปี
- ในการทำงานของท่าน ท่านมีการสวมถุงมือในการทำงานหรือไม่
  - ☐ ไม่มี
  - ☐ มี โปรดระบุชนิด เช่น ถุงมือยาง ถุงมือผ้า ถุงมือหนัง เป็นต้น . . . . . .

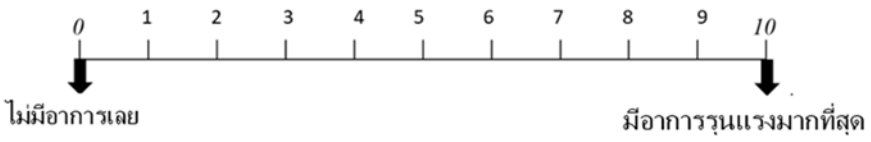
หากท่านมีการสวมถุงมือขณะทำงาน โปรดระบุระยะเวลาที่มีการสวมถุงมือ/วัน

☐ น้อยกว่า 2 ชั่วโมง ☐ 2 ชั่วโมง ☐ มากกว่า 2 ชั่วโมง

ความรุนแรงของปัญหาผิวหนังที่มือของท่าน

ระดับอาการคัน/แสบ หรือ เจ็บปวด ของผื่นผิวหนัง **ช่วงที่เป็นมากที่สุด**

ความรุนแรงของผื่น **ณ ปัจจุบันนี้**



ระดับอาการคัน/แสบ หรือ เจ็บปวด ของผื่นผิวหนัง **ณ ปัจจุบันนี้**

ความรุนแรงของผื่น **ณ ปัจจุบันนี้**

WK	วันที่
NO.	
HN	

	ถ่ายรูป		
	ชั่งครีม	ซ้าย..... g	ขวา .....g
	จำนวน cotton bud	ซ้าย.....	ขวา .....

แบบฟอร์มข้อมูล (Case record form) สำหรับแพทย์ผู้ประเมิน

1. Criteria

Inclusion criteria	Yes	No
- Symmetrical chronic hand eczema (Duration > 3 months or Recurrent ≥ 2 episodes / year)		
- Age ≥ 20 years		
- Mild to moderate PGA severity		
- Subjects are able to sign inform consent form		
Exclusion criteria		
- Have other dermatologic conditions on their hands		
- Known allergy to calcipotriol or Vaseline ointment		
- Have serious systemic diseases		
- Use of topical treatment on their hand within the last 2 weeks		
- Use of systemic treatment within the last 4 weeks		
- For female: pregnancy or lactation		

2. Hand eczema type of subject

☐ Chronic fissured hand eczema

☐ Recurrent vesicular hand eczema

☐ Hyperkeratotic palmar eczema

☐ Pulpitis

☐ Interdigital eczema

☐ Nummular hand eczema

3. ข้อมูลเพิ่มเติมของผู้ป่วย

3.1 Underlying diseases ☐ no ☐ yes

☐ Atopy ☐ Any dermatitis ☐ Asthma ☐ Diabetes mellitus

☐ Kidney disease ☐ Others . . . . . .

In allergy case, how did the patient be diagnosed?

☐ Skin test ☐ Diagnosed by doctor without skin test ☐ others . . . . . .

3.2 Any drug allergy ☐ no ☐ yes (detail) . . . . . .

3.3 Any food allergy ☐ no ☐ yes (detail) . . . . . .

3.4 Current medication ☐ no ☐ yes (detail) . . . . . .

3.5 Current topical application on hands ☐ no ☐ yes (detail) . . . . . .

How long has the patient been having hands dermatitis? . . . . . .months/years

or intermittent . . . . . times/year

3.6 Previous treatment

Topical treatment	yes	no	Name of agent
Emollients			
Topical steroids			
Topical calcineurin inhibitor			
Topical Vitamin D analogue			
Others			
Systemic treatment	yes	no	Name of agent
Systemic corticosteroid			
Retinoid receptor agonist			
Systemic immunomodulator			
Others			
Physical treatment	yes	no	Name of agent
UVB			
PUVA			

Others . . . . . .

Where did the patients get the above treatment from? . . . . . .

3.7 Does the patients have any dermatitis in other area?

☐ Foot ☐ Flexor area ☐ scalp ☐ other area . . . . . .

3.8 What does the patient think was the cause of the eczema or make the eczema even worse?

	Yes	No
• Major activities at work	☐	☐
• Personal hygiene product	☐	☐
eg. soap, shampoo etc.	☐	☐
• Household cleaning product	☐	☐
• Laundry products	☐	☐
• Frequent hand washing	☐	☐
• House work	☐	☐
eg. gardening, handling of food, etc.		
• Protective gloves	☐	☐
(What kind of gloves? . . . . . .)		
• Others		

What is/are the reason(s) of the answer above? (eg. The eczema started or got worse during working day or started using the suspected product, The eczema got better or cleared during vacation or stop using suspected product.) . . . . . .

3.9 How often does the patient contact with wetwork?

☐ 0 day ☐ 1-3 day(s)/week ☐ 4-6 days/week ☐ Every day

PGA-mTLSS Left…….. Right ……..

PGA Severiy	Features	Intensity	Are involved
Severe	Erythema, scaling, hyperkeratosis/ lichenification Vesiculation, oedema, fissure, pruritus/pain	At least 1 moderate or severe At least 1 severe	>30% of hand surface
Moderate	Erythema, scaling, hyperkeratosis/ lichenification Vesiculation, oedema, fissure, pruritus/pain	At least 1 mild or moderate At least 1 moderate	10-30% of hand surface
Mild	Erythema, scaling, hyperkeratosis/ lichenification Vesiculation, oedema, fissure, pruritus/pain	At least 1 mild At least 1 mild	<10% of hand surface
Almost clear	Erythema, scaling, hyperkeratosis/ lichenification Vesiculation, oedema, fissure, pruritus/pain	At least 1 mild Absent	<10% of hand surface
Clear	Erythema, scaling, hyperkeratosis/ lichenification Vesiculation, oedema, fissure, pruritus/pain	Absent Absent	Not detectable

Parameter	Description of severity
Erythema	0 = Absent 1 = Faint erythema 2 = Prominent redness 3 = Deep intense red color
Scaling	0 = Absent 1 = Slight flaking over limited areas, mostly fine scales 2 = Flaking over widespread area(s), coarser scales 3 = Desquamation covering over 30% of the hand, with coarse thick scales
Lichenification/hyperkeratosis	0 = Absent 1 = Mild thickening with exaggerated skin lines over limited areas 2 = Palpable thickening over widespread area(s) 3 = Prominent thickening over widespread area(s) with exaggeration of normal skin markings
Vesiculation	0 = Absent 1 = Scattered vesicles affecting up to 10% of hand, without erosion 2 = Scattered or clustered vesicles affecting up to 30% of hand, without visible erosion or excoriation 3 = High density of vesicles extending over large area(s), or with erosion or excoriation
Oedema	0 = Absent 1 = Dermal swelling over less than 10% of hands 2 = Definite dermal swelling over more thar 10% of hand, 3 = Dermal swelling with skin induration over widespread area(s)
Fissures	0 = Absent 1 = Cracked skin affecting a small area of the hand 2 = Cracked skin affecting multiple areas of the hand and causing pain 3 = One or more deep fissures and causing bleeding or severe pain
Pruritus/pain	0 = Absent 1 = Occasional, slight discomfort a few times per day 2 = Intermittent, causing discomfort frequently during the day 3 = Persistent or interfering with sleep
1 = mild; 2 = moderate; 3 = severe.	

4.2 Hand eczema severity index (HECSI) score

Erythema (E), Infiltration/papulation (I), Vesicles (V), Fissures (F), Scaling (S), Oedema (O)

Clinical signs	(E)	(I)	(V)	(F)	(S)	(O)	Total clinical score	Extent (Ex)	HECSI Scores
Fingertips									
Finger (except tips)									
Palm of hand									
Back of hand									
Wrists									
								Total HECSI Score =	

Clinical signs	(E)	(I)	(V)	(F)	(S)	(O)	Total clinical score	Extent (Ex)	HECSI Scores
Fingertips									
Finger (except tips)									
Palm of hand									
Back of hand									
Wrists									
								Total HECSI Score =	

The intensity of 6 clinical signs are scored as 0 : no skin changes, 1 : mild disease, 2 : moderate disease, 3 : severe disease.

The affected area are scored as 0: 0%, 1: 1%-25%, 2: 26%-50%, 3: 51%-75%, 4: 76%-100%.

WK วันที่
NO.
HN

	ถ่ายรูป		
	จำนวนcotton bud	ซ้าย.....	ขวา .....

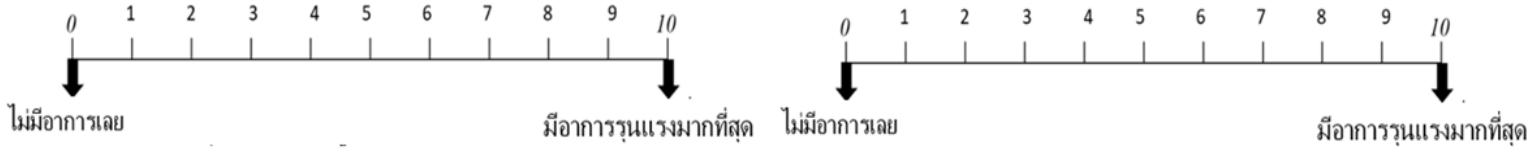
แบบฟอร์มข้อมูล (Case record form) สำหรับผู้เข้าร่วมการวิจัย

1) กรุณาระบุความรุนแรงของปัญหาผิวหนังที่มือของท่านในช่วงเวลาต่างๆตามแผนภาพด้านล่าง (โดยกากบาททับระดับความรุนแรงที่ท่านเลือก) เริ่มจาก 0 - 10 คะแนนโดยที่ 0 หมายถึงไม่มีอาการเลย และ10 คือรุนแรงมาก

ระดับความรุนแรงของผื่น **<u>ช่วงที่เป็นมากที่สุด</u>**

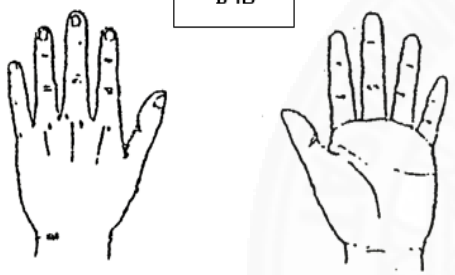
ความรุนแรงของผื่น **<u>ณ ปัจจุบันนี้</u>**

หลังจากท่านเข้าร่วมการวิจัยและใช้ตัวยาในการรักษาผื่นที่มือ ท่านมีอาการเหล่านี้หลังจากใช้ยาหรือไม่



หลังจากท่านเข้าร่วมการวิจัยและใช้ตัวยาในการรักษาผื่นที่มือ ท่านมีอาการเหล่านี้หลังจากใช้ยาหรือไม่

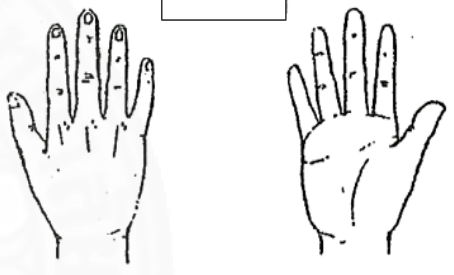
ซ้าย



อาการ	ไม่มี	มี		
		เล็กน้อย	ปานกลาง	รุนแรง
แดง				
แสบ/ร้อน				
บวม				
ลอก				

ระยะเวลาที่มีอาการข้างต้น .....

ขวา



อาการ	ไม่มี	มี		
		เล็กน้อย	ปานกลาง	รุนแรง
แดง				
แสบ/ร้อน				
บวม				
ลอก				

ระยะเวลาที่มีอาการข้างต้น .....

WK	วันที่
NO.	
HN	

	ถ่ายรูป		
	จำนวนcotton bud	ซ้าย.....	ขวา .....

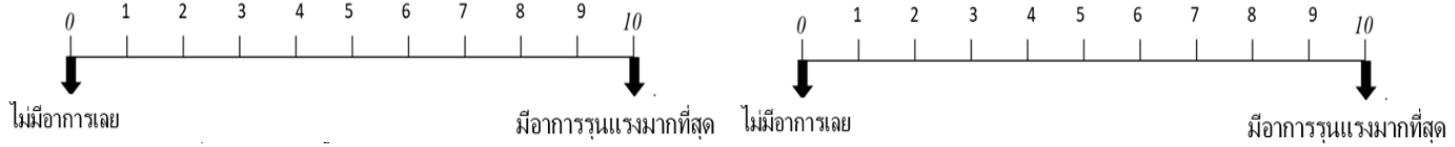
แบบฟอร์มข้อมูล (Case record form) สำหรับผู้เข้าร่วมการวิจัย

1) กรุณาระบุความรุนแรงของปัญหาผิวหนังที่มือของท่านในช่วงเวลาต่างๆตามแผนภาพด้านล่าง (โดยกากบาททับระดับความรุนแรงที่ท่านเลือก)
เริ่มจาก 0 - 10 คะแนนโดยที่ 0 หมายถึงไม่มีอาการเลย และ10 คือรุนแรงมาก

ระดับความรุนแรงของผื่น **<u>ช่วงที่เป็นมากที่สุด</u>**

ความรุนแรงของผื่น **<u>ณ ปัจจุบันนี้</u>**

หลังจากท่านเข้าร่วมการวิจัยและใช้ตัวยาในการรักษาผื่นที่มือ ท่านมีอาการเหล่านี้หลังจากใช้ยาหรือไม่



2) Quartile grading scale : Circle the percent improvement

Patient's self-assessment

Improvement	0	1-25%	26-50%	51-75%	>75%
Score	0	1	2	3	4

Dermatologists' assessment

Improvement	0	1-25%	26-50%	51-75%	>75%
Score	0	1	2	3	4

3) Adverse reaction

อาการ	ไม่มี	มี		
		เล็กน้อย	ปานกลาง	รุนแรง
แดง				
แสบ/ร้อน				
บวม				
ลอก				

ระยะเวลาที่มีอาการข้างต้น .....

อาการ	ไม่มี	มี		
		เล็กน้อย	ปานกลาง	รุนแรง
แดง				
แสบ/ร้อน				
บวม				
ลอก				

ระยะเวลาที่มีอาการข้างต้น .....

BIOGRAPHY

Name	Ratchasin Pongprasert, M.D
Date of Birth	May 28, 1987
Educational	Academic Year 2011: The Degree of Doctor of Medicine Faculty of Medicine Thammasat University, Thailand
Work Position	2012-2013 First year internship at Nakhon Nayok hospital, Nakhon Nayok
	2013-2015 Second – Third year internship at Ongkarak hospital, Nakhon Nayok