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ORIGINAL ARTICLE

2020 Korean Consensus Guidelines for Diagnosis and Treatment of Chronic Hand Eczema

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Background: Hand eczema refers to eczema located on the hands, regardless of its etiology or morphology. Despite its high prevalence and significant impact on patients' quality of life, treatment is frequently challenging because of its heterogeneity, chronic and recurrent course, and lack of well-organized randomized controlled trials of the various treatment options. **Objective:** These consensus guidelines aim to provide evidence-based recommendations on the diagnosis and management of hand eczema to improve patient care by helping physicians make more efficient and transparent decisions. **Methods:** A modified Delphi method, comprising two rounds of email questionnaires with face-to-face meetings in between, was adopted for the consensus process that took place between February and September 2020. Forty experts in the field of skin allergy and contact dermatitis were invited to participate in the expert panel. **Results:** Consensus was reached for the domains of classification, diagnostic evaluation, and treatment; and a therapeutic ladder to manage chronic hand eczema was developed. **Conclusion:** These are the first consensus guidelines for chronic hand eczema in the Asian population, which will help standardize care and assist clinical decision-making in the diagnosis and treatment of chronic hand eczema. **(Ann Dermatol 33(4) 351~360, 2021)**

-Keywords-
Asian population, Chronic hand eczema, Consensus guidelines

INTRODUCTION

The word "eczema" encompasses various inflammatory skin diseases with common histologic and clinical manifestations. Histologic hallmarks include spongiosis and exocytosis in the acute stage, followed by hyperkeratosis and acanthosis in the chronic stage[1,2]. Representative clinical features are redness, vesicles, erosions, scales, thickening, and fissures[3]. "Eczema" and "dermatitis" are often used interchangeably[1], and in this report, we use "eczema" consistently throughout. Hand eczema refers to eczema located on the hands, regardless of its etiology or morphology. It is relatively common, with a lifetime prevalence of 15%~31%, depending on the study population. Hand eczema affects both sexes and all age groups, but it is more prevalent among people in their twenties and thirties, and females are twice more affected than males, likely influenced by exposure patterns[4-8].

Mild and acute hand eczema is usually controlled by applying moisturizers and topical corticosteroids, and avoid-

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ing potential irritants[9]. However, when hand eczema becomes persistent and refractory to the standard regimen, it can be debilitating and significantly reduce patients' quality of life, causing occupational, functional, social, and psychological disabilities[2,10,11]. Chronic hand eczema is often defined as an eczematous process on the hands lasting for more than three months or relapsing twice or more per year[1,12]. It is estimated that 5%～7% of patients with hand eczema develop severe chronic hand eczema, and 2%～4% are unresponsive to standard treatment[13]. However, evaluation and management of hand eczema is hindered by the lack of a uniform classification system and controlled therapeutic trials. Guidelines from different groups vary considerably regarding classification and management recommendations[1,6,14-16]. The diagnostic predicament in hand eczema stems mainly from the fact that clinical manifestations and histologic features of skin lesions on the hands can be very similar, regardless of etiology. Meanwhile, pathogenesis can be multifactorial, making it difficult to specify the cause[9]. Consequently, most classification systems reflect a combination of appearances, history of coexistent illnesses, and irritant and allergen exposure status.

Clinical practice guidelines are developed to improve patient care by providing evidence-based recommendations[17]. They help physicians make decisions more efficiently and transparently by analyzing research findings and inter-expert agreements. Consensuses are built based on systematic literature reviews and structured professional consultations, in relevance to the local situation. Distinct genetic, environmental, social and cultural factors are present in different ethnicities and countries. However, the target populations in previous guidelines and recommendations were predominantly white and not racially diverse[1,6,14-16]. Therefore, this working group was dedicated to developing clinical guidelines for chronic hand eczema in the Asian population.

MATERIALS AND METHODS

The guideline development working group, a representative group on behalf of the Korean Society of Contact Dermatitis and Skin Allergy, comprised 5 core members who executed a systematic review of the literature and organized the guideline development process. The working group invited 40 experts in the field of skin allergy and contact dermatitis to serve as the expert panel.

Literature review

MEDLINE, from 1990 to January 2020, and Cochrane Database of Systematic Reviews, from 2000 to January 2020, were searched for English-language literature to identify evidence of best practices to develop clinical guidelines. The search strategy combined titles and keywords including "hand eczema" or "hand dermatitis" and "screening" or "evaluation" or "diagnosis" and "treatment" or "intervention" or "management". Classification, diagnostic evaluation, and treatment were selected as questionnaire domains.

Consensus process

A modified Delphi method comprising two rounds of email questionnaires and face-to-face meetings (prior to, between, and after email surveys) was adopted for the consensus process that took place between February and September 2020.

In round 1, panelists were asked to provide their opinion for each item as 1) "agree" or "disagree," 2) level of agreement (0～10 points), and 3) free comments. Of the 40 invited panel members, 30 participated in the first round of the survey (75% response rate). The consensus for each item was categorized as "consensus-in," "discussion-required," or "consensus-out." "Consensus-in" was defined as ≥70% of participants agreeing with a survey statement, with an average agreement score of ≥7. An item agreed by ≥70% of participants, but with an average agreement score of <7, was classified as "discussion-required" and further discussed in the following face-to-face meeting. Those that did not meet the threshold for "consensus in" or "discussion-required" were classified as "consensus-out" and excluded from the second round of the survey. Accordingly, the working group revised the statements for the second round of the survey, in which all participants were informed of the results from the first round. In round 2, the panelists were asked: 1) whether they agreed with the statement, 2) to prioritize the items, 3) to define specific treatment periods, and/or 4) free comments depending on the question items. Of the 40 invited panel members, 26 participated in the second round (65% response rate). The consensus was defined either as ≥70% agreement or the 3 items with the highest prioritization ranking.

RESULTS AND DISCUSSION

Classification

Hand eczema is often polymorphic, and its morphology is not specifically related to its etiology, which is sometimes ambiguous and often multifactorial. A variety of terms have been used to describe the various clinical manifestations of hand eczema. A provisional classification system developed from the literature review was presented to the expert panel (Supplementary Table 1).

1) Consensus process

In round 1, all classification items were categorized as consensus-in, except for contact urticaria/protein contact dermatitis and pustular dermatitis, which were categorized as discussion-required. After discussion among the working group, contact urticaria/protein contact dermatitis was excluded from the classification system; pustular dermatitis was incorporated into vesicular type; and pulpitis was distinguished from hyperkeratotic dermatitis. As additions to the originally proposed classification system, "unclassified" was added as an etiologic subtype representing those cases in which a specific etiology cannot be identified, and "mixed" was added as a morphologic subtype representing those cases in which multiple morphologic subtypes are present without one being predominant. Due to the etiologic and morphologic heterogeneity of chronic hand eczema, its classification primarily relies on the prevailing features at the time of diagnosis. The revised classification system is detailed in Table 1. The agreement rate in round 2 was 88.5%.

2) Definitions

Prolonged exposure to irritants causes irritant hand eczema, and the duration and intensity of exposure contribute to the development of eczema. Meanwhile, irritant dermatitis can make patients susceptible to allergic sensitization to antigens that would not normally cause dermatitis on non-inflamed skin[18]. Therefore, concurrence of irritant and allergic hand eczema is common.

Allergic hand eczema is a delayed type hypersensitivity caused by contact with an allergen in a sensitized individual. A positive patch test and relevant current allergen exposure confirm the diagnosis, although relevance can be either suspected or proven[1,18].

Atopic hand eczema is chronic hand eczema in individuals with previous or current atopic dermatitis, without relevant exposure to irritants or allergens. An epidermal barrier defect observed in atopic dermatitis occasionally predisposes patients to develop irritant-type hand eczema[19,20].

Pompholyx (vesicular dermatitis) presents as symmetric, firm, deep-seated vesicles on the palms and the sides of the fingers, together with redness and severe pruritus. Episodes typically last 2 to 3 weeks, followed by resolution with thick desquamation, but recurrences are typical.

Hyperkeratotic hand eczema, in a narrow sense, is limited to endogenous eczema characterized by hyperkeratosis, classically presenting as sharply demarcated circumscribed hyperkeratotic and fissured lesions without vesicles in the center of the palms[1,14,21,22]. However, other types of hand eczema, particularly irritant type, can eventually become hyperkeratotic, lichenified, and fissured[23].

Pulpitis is hyperkeratotic eczema mainly occurring on the fingertips, occasionally accompanied by fissures and vesicles[16].

Diagnostic evaluation

Hand eczema is not a single homogeneous entity, requiring a combination of appropriate diagnostic efforts. Various diagnostic measures, including detailed history taking, physical examination, and diagnostic tests, were presented in the survey (Supplementary Table 2). In round 1, the skin prick test, measurement of serum total im-

Table 1. Classification of chronic hand eczema

Classification	Definition
Etiologic	
Irritant contact dermatitis (ICD)	Documented exposure of the hands to an irritant, which is likely to cause contact dermatitis, with no relevant contact allergy (no current exposure to allergens to which the patient has reacted positively in a patch test)
Allergic contact dermatitis (ACD)	Hand eczema caused by relevant contact allergens or cross-reactors identified by patch testing (relevance meaning that there is current exposure of the hands to the allergen)
Atopic hand eczema	Hand eczema in a patient with a history of atopic eczema, previous or current, with no documented irritant or relevant allergen exposure likely to cause eczema
Unclassified	The cause cannot be specified
Morphologic	
Hyperkeratotic eczema	Chronic eczema with hyperkeratosis on the palms and fingers, without vesicles or pustules
Pompholyx (vesicular dermatitis)	Recurrent hand eczema with vesicular or vesiculopustular eruptions
Pulpitis (fingertip eczema)	Hyperkeratotic eczema on the fingertips, possibly with fissures extending under the nails, especially on the thumbs and middle fingers (although it may affect all fingers); vesicles may occasionally be observed
Mixed	Multiple morphologic types are mixed without any one specific predominant type

munoglobulin E (IgE) level, microbial tests, and skin biopsy were categorized as "discussion-required," while all others were categorized as "consensus-in." After discussion among the working group, the skin prick test was excluded from the list of essential diagnostic measures, and the other tests were retained in round 2 of the survey.

In round 2, panelists were asked to propose specific clinical indications for each diagnostic evaluation (Table 2). Comprehensive history taking and physical examination were suggested to be essential for all patients with chronic hand eczema. Hand eczema-related history includes patterns, evolution, and duration of symptoms; exacerbating or relieving factors; recurrence rate; and details of exposure history specific to current clinical manifestations. Other past medical history, such as atopic disorders (asthma and allergic rhinitis), endocrine and autoimmune diseases, can provide practical clues. Everyday life-related history, including exposure in home or work settings, hobbies, and frequency of wet work, can also be useful. Family history information is helpful in determining patients' atopic diathesis and identifying hereditary disorders, such as familial palmoplantar keratoderma.

Not only the hands but the entire skin should be inspected, especially the feet. Palmar psoriasis, and palmoplantar pustulosis are important differential diagnoses of the hyperkeratotic and vesiculopustular variants. Careful inspection for dermatophytosis is also vital to differentiate id reaction[1]. Thorough physical examination, history taking, and total IgE level testing aid in identifying atopic dermatitis.

It was suggested that diagnostic procedures should be individualized for each case, led by the findings of history taking and clinical examination. Additionally, panelists stated that they would consider performing procedural diagnostic tests when lesions were unresponsive or only partially responsive to standard treatment.

Diagnostic patch testing was recommended for cases when the clinical picture is indicative of allergic contact dermatitis, and when hand eczema lasts more than three months to identify the role of contact allergens in the environment[1]. It is important to include relevant "as is" substances as well as the baseline series. A negative patch test does not definitively exclude an allergy, because false negative results can occur. Complete avoidance of the allergen is integral to clearing allergic hand eczema and replacement of the causative allergen with a safe alternative is beneficial; thus, it is important to assess the relevance of identified allergens and patients must be educated about their identified allergens.

Serum total IgE measurement is valuable, particularly when type I hypersensitivity is suspected, or when a search for atopic diathesis is indicated.

Microbial tests to identify infectious causes, including bacteria, fungi, and viruses, are considered depending on clinical manifestations. Infections can also be an aggravating or triggering factor. Patients with atopic dermatitis are particularly susceptible to secondary bacterial infections[24,25]. Verification of fungal infection is helpful for differentiating tinea manuum and identifying autosensitization with fungal infection in the feet. Scabies is another important differential diagnosis that needs to be excluded.

Skin biopsy can also be useful, although chronic inflammatory skin diseases may show non-specific histologic features, not allowing sufficient distinction for a con-

Table 2. Diagnostic evaluation methods for chronic hand eczema

Diagnostic evaluation method	Detail
Hand eczema-specific medical history	Duration, recurrence, exposure, etc.
Past medical history	Atopic, endocrine, autoimmune disorders, etc.
Exposure history	Work, hobbies, daily life
Family history	Atopic diathesis To differentiate familial disorders, such as familial palmoplantar keratoderma
Physical examination Presence of skin lesions on areas other than hands	Location, morphology, etc.
Patch test	To identify contact allergen When lesions are unresponsive to standard treatment
Serum total Immunoglobulin E level	With atopic diathesis (atopic dermatitis, asthma) When suspicious of allergen sensitization and type 1 hypersensitivity
Microbial tests (bacterial, fungal, viral, and helminth)	When infectious cause is suspected When lesions are unresponsive to standard treatment
Skin biopsy	To differentiate other skin disorders involving palms, such as psoriasis and palmoplantar pustulosis When lesions are unresponsive to standard treatment

clusive diagnosis. Common dermatoses affecting the hands that can resemble chronic hand eczema, both clinically and histologically, include psoriasis, lichen planus, keratoderma, fungal infection, and scabies infestation, when scales and keratosis predominate; and palmar pustulosis, fungal infection, and scabies infestation, when vesicles and pustules predominate.

Treatment

Treatment of hand eczema must account for disease etiology (atopic, allergic, irritant), acuteness (acute vs. chronic), morphology (redness, scaling, lichenification, vesicles, etc.), and location (dorsal aspects of hands, interdigital spaces, palms)[1]. Evidence for a standardized regimen to control chronic hand eczema is very limited, and the quality is mainly moderate because most analyses were based on single studies with small sample sizes. Furthermore, a large variety of treatments were compared to various options, including no treatment, variants of the same medication, placebo, or vehicle[26]. Few studies have compared two different classes of interventions. The working group chose better corroborated and accessible treatment options to be included in the consensus process (Supplementary Table 3). Psoralen with ultraviolet A (PUVA) was not included because neither topical nor oral psoralen is available in Korea.

In round 1, it was suggested to limit the use of systemic corticosteroid to "short-term". The definition of short-term use of systemic corticosteroids was surveyed in round 2. Other systemic therapy (e.g., azathioprine) and ultraviolet (UV) A phototherapy were excluded because of a low agreement rate. Biologics were excluded following the discussion of the working group. Although dupilumab is approved for severe atopic dermatitis, atopic eczema limited to the hand is still not an indication. Since there is an ongoing phase 2 clinical trial to evaluate whether dupilumab is effective for moderate to severe chronic hand eczema refractory to potent topical corticosteroids (NCT03861455)[27], it remains to be seen. Guselkumab was initially approved for moderate-to-severe psoriasis and palmoplantar pustulosis[28,29]. Because pustules occasionally appear in hand eczema, particularly impetiginized or vesiculopustular type, palmar pustulosis is an important and challenging differential diagnosis of chronic hand eczema; however, guselkumab is not indicated for chronic hand eczema.

In round 2, panelists were asked to prioritize therapeutic measures to provide an overview of proposed stepwise treatment depending on treatment response. Basic skin protection, elimination of potential causative exogenous factors, and intensive use of moisturizers were suggested as integral components of treatment in all patients with hand eczema. Other pharmacologic interventions were added to construct a therapeutic ladder (Fig. 1).

Routine skin care and protection are fundamental as a non-pharmacological intervention as well as for prevention of chronic hand eczema. This covers the rigorous elimination of confirmed irritants and allergens, aided by substituting alternatives when possible; use of protective measures; and application of moisturizers. Patients need to understand that chronic hand eczema is frequently only controllable and not curable; thus, patient education should build realistic expectations regarding prognosis.

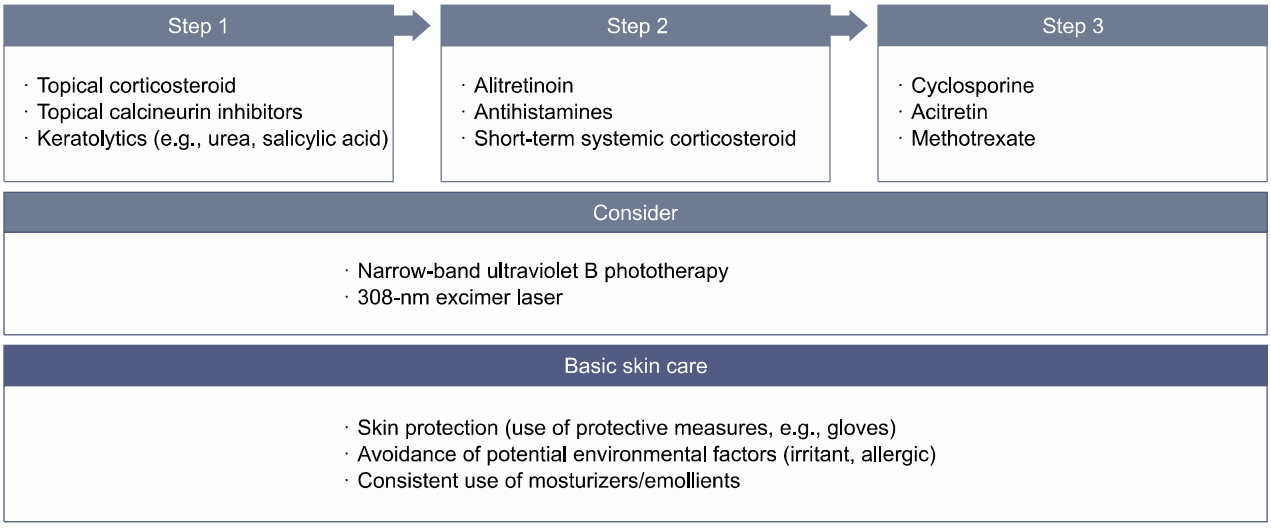

Fig. 1. Suggested therapeutic ladder for chronic hand eczema. Basic skin protection, avoidance of potential exogenous irritants and allergens, and intensive use of moisturizers are the keystones for managing chronic hand eczema. Topical and systemic medication, and phototherapy are integrated into a stepwise therapeutic approach.

Despite the universal consensus among dermatologists regarding the importance of moisturizers, data on their effect in chronic hand eczema are surprisingly sparse. There are no established data comparing the effects of the various compositions and formulations, such as oil-in-water, water-in-oil, and gels[26,30]. Therefore, the guideline development group cannot provide specific recommendations on which type of moisturizer should be used. In general, moisturizers are recommended for prophylaxis and barrier repair[1].

Wearing gloves is another good strategy to protect skin[18,31]. However, occlusion alone can aggravate inflammation in already-irritated skin, thus occlusive gloves should be used for the shortest time possible[1,32]. Components of rubber products, such as carba mix and thiuram mix, can induce allergic contact hand eczema[33-35].

Topical corticosteroids are the local treatment of choice for hand eczema[36]. They are effective for brief use, but side effects of epidermal atrophy and interfered skin recovery limit their chronic use[37,38]. Allergy to corticosteroids is not uncommon and should be considered when hand eczema does not respond to treatment[1,39]. Although intermittent dosing of corticosteroids, or substituting or combining with a topical calcineurin inhibitor, is clinically suggested to reduce adverse events, there is no corroborating evidence yet[1].

Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are non-steroidal immunomodulators that inhibit production and release of inflammatory mediators. They are approved for treatment of atopic dermatitis when topical corticosteroids have failed or are not tolerated. A within-participant study showed that both 0.1% tacrolimus and 0.1% mometasone furoate were effective and well-tolerated for vesicular hand eczema[40].

Keratolytics, such as salicylic acid at a concentration of up to 20% and urea at concentrations of 5% to 10%, reduce hyperkeratosis with softening and penetration-enhancing effects[15]. Excessive amounts or simultaneous exposure to an irritant can cause skin irritation; thus, keratolytics should be cautiously used depending on clinical manifestations.

Severe chronic hand eczema that does not sufficiently respond to local therapy may require systemic treatment. Alitretinoin is currently the only licensed medication specifically for severe chronic hand eczema refractory to topical corticosteroids[9,41,42]. It is a retinoid with anti-proliferative, anti-inflammatory, and immunomodulatory but not immunosuppressive effects[43,44]. The time to response was significantly shorter with alitretinoin 30 mg than 10 mg, and when combined with a topical corticosteroid, the result was clinically rapid and superior to alitretinoin monotherapy[9,45]. Since relapses were successfully treated with re-administration of alitretinoin[46], intermittent use of alitretinoin could be suitable for long-term management of chronic hand eczema. Differences in the efficacy regarding morphologic or etiologic subtypes are controversial: some studies reported that alitretinoin was effective for all morphologic subgroups, whereas others reported that hyperkeratotic type responded more readily than vesicular type[9,47]. The working group recommends alitretinoin for patients with severe chronic hand eczema refractory to topical corticosteroids.

Systemic corticosteroids can be used short-term to control acute severe hand eczema, but are not appropriate for long-term use because of their well-known systemic side effects, including hypothalamic-pituitary-adrenal axis suppression, hyperglycemia, and osteoporosis. However, when chronic hand eczema is complicated with acute exacerbation, short-term use of systemic corticosteroids can be effective. In the current guideline development process, "short-term" use of systemic steroids was defined as a 2-week period.

Recent guidelines criticize the use of antihistamines in the management of chronic hand eczema, largely because of the lack of trial-based evidence[1,15]. However, antihistamines are widely prescribed to control hand eczema, primarily for their anti-pruritic and anti-inflammatory properties[48]. Similarly, in this guideline development process, use of antihistamines was agreed upon by 96.7% of participating panelists. The lack of trial-based evidence does not negate their therapeutic potential. Further quantitative and qualitative studies are necessary to standardize their use in chronic hand eczema. The guideline core working group recommends antihistamines as an adjunct second-line treatment for chronic hand eczema.

There is moderate evidence for the use of cyclosporine in chronic hand eczema[26]. In a double-blind study, oral cyclosporine (3 mg/kg/day) for 6 weeks was slightly better than 0.05% betamethasone dipropionate cream (50% versus 32% decrease in disease activity)[49]. In an open-label study, one-year success rates were 74% after 6-week treatment with oral cyclosporine 3 mg/kg/day[50]. Potential adverse events, such as hypertension and impaired renal function, are major factors limiting its use. The working group recommends cyclosporine as a third-line treatment for patients with severe chronic hand eczema refractory to or relapsing after topical treatment, alitretinoin, and systemic corticosteroids.

Acitretin, another retinoid distinct from alitretinoin has limited data on its efficacy. In a small open-label study, 51% symptoms of hyperkeratotic dermatitis of the palms were reduced with 30 mg/day acitretin for four weeks, compared to 9% with a placebo. Interpretation of this data

requires caution because psoriasis was included in this study[51]. The working group suggests that acitretin could be considered in predominantly hyperkeratotic type that is refractory to other topical and systemic treatments.

Anecdotal evidence showed that low doses of methotrexate can be effective in recalcitrant hand eczema, reducing the need for concomitant systemic corticosteroids[52]. Considering its effects in other chronic inflammatory skin conditions, such as atopic dermatitis and psoriasis, methotrexate could be recommended as a third-line treatment[53].

UV phototherapy with various wavelengths is moderately supported[26]. Despite evidence for PUVA and broadband UVB therapy, the unavailability of psoralen and uncommon use of broadband UVB systems in Korea limited this guideline review to narrowband UVB (NB-UVB) and 308-nm excimer laser[54]. In a small open-label study, although none achieved clearance during the 10-week treatment, 18 of the 26 patients were defined as much improved[55]. Similarly, 308-nm excimer laser is useful to locally irradiate a small focal area of the hand[56,57]. The guideline working group recommends phototherapy as an auxiliary treatment in addition to other topical or systemic treatments.

Originally, surveys were performed regarding therapeutic approaches according to disease severity (evaluated by physician global assessment, assisted by clinical photos), and definition of the treatment period to evaluate treatment response. However, these items were excluded in the final process: only the definition of short-term systemic corticosteroid treatment (2 weeks) was retained. Although disease severity is a crucial factor signifying therapeutic efficacy, there is still no consistent severity scoring system;[9,58-62] thus, analyzing treatment regimens according to severity seemed to be premature at this point. In addition, it was proposed that the timeframe to assess therapeutic efficacy should be individualized for each therapeutic measure. For example, alitretinoin can be trialed for 12 to 24 weeks, while the use of systemic steroids should be limited to a short period[9,41]; thus, flat application of a uniform treatment period for all therapies was considered inappropriate.

Future directions

Evaluation of disease severity is crucial for a diagnosis and assessment of treatment efficacy. However, currently available guidelines for chronic hand eczema, including ours, do not account for severity. This may be due to the lack of a universal severity scoring system that is clinically practical and easy to use. Although various severity scores, such as physician global assessment, modified total lesion symptom score, Hand Eczema Area Severity, and the Clinical Photo Guide, have been developed, none have gained unanimous approval, and different studies and clinical trials have used different severity systems[9,58-62]. Morphologic variety and confusing classification system are the main issues. Severity scoring is typically based on visible factors, and it is still not known if the scoring system for chronic hand eczema should differ depending on the subtype or if a universal scoring system could be applicable to every subtype. Thus, further efforts to develop practical severity scores, and incorporation of severity in guidelines for hand eczema, are warranted.

These are the first guidelines for hand eczema in the Asian population, which will help standardize care and assist clinical decision-making in the diagnosis and treatment of chronic hand eczema.

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SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/src/sm/ad-33-351-s001.pdf

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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