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The Symptom Characteristics and the Efficacy of Combining Therapies in Inpatients with Atopic Dermatitis: A Study on Vietnamese Population

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Abstract

BACKGROUND: At present, biologics and targeted disease-modifying therapies were developed to provide an effective control for adult with moderate-to-severe atopic dermatitis.

AIM: This study aimed to describe clinical features, stages, and severity levels of the disease as well as to evaluate the therapeutic efficacy of combining therapies in adults with atopic dermatitis.

METHODS: One hundred and twenty-eight patients with atopic dermatitis diagnosis based on the Rajka and Hanifi standards at the Inpatient Department of Can Tho Dermato-Venereology Hospital from May 2018 to May 2020 were recruited in this study. The clinical characteristics were recorded. The treatment response was evaluated through the improvement of clinical presentations and the altering SCORing Atopic Dermatitis score (SCORAD).

RESULTS: The study showed that people aged 60 and over made up the largest proportion of total investigated patients. Pruritus was the predominant symptom of atopic dermatitis. There was an association between xerosis symptom and disease severity. After 2 weeks of treatment, the mean of SCORAD score significantly decreased by more than half. In addition, 88.4% of patients showed an excellent response and there was no patient with none/poor improvement.

CONCLUSION: Our study supports that the combination of therapeutic methods might reduce symptoms in atopic dermatitis patients, and thereby improving their quality of life.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory disease accounting for 0.02%–8.10% in adults [1], [2]. AD's prevalence, clinical presentation, severity, health-care accessibility varies among populations, reflecting multifactorial interactions between genetic, immune, and environmental features in AD [3], [4]. Although the pathogenesis of AD has not been completely elucidated, the previous studies showed that it related to genetic factors and allergens such as food, respiratory, exposure, climate change, and infection [5], [6].

Clinical presentations of AD are featured by pruritus and eczematous lesions. First, severe itching leads to the establishing of the itch-scratch cycle, which has a significant impact on patients' quality of life [7], [8]. In addition, the patterns of lesions have three stages including acute lesions (erythematous papules and erythema), subacute lesions (erythematous and excoriated scaling papules), and chronic lesions (thickened skin, lichenification, and fibrotic papules). All three types of lesions can be found in the same individual and often overlap, making the treatment of the disease challenging [6], [9].

SCORing Atopic Dermatitis index (SCORAD) is a good tool for assessing the severity of atopic dermatitis because the score obtained from SCORAD can reflect the duration of the lesion as well as the degree of improvement during and after treatment [10], [11]. In a study comparing the reliability and reproducibility of measuring AD severity methods, Bożek and Reich reported that the SCORAD had the highest inter-rater reliability [12]. Besides, a study suggested that the SCORAD was a useful tool for evaluating the effectiveness treatment of oral probiotics and topical corticosteroids in patients with moderate AD [13]. Another study also observed that dupilumab resulted significant and sustained advances in SCORAD outcomes in adult with moderate-to-severe AD [14].

AD relapses can be controlled with moistures, bathing practices, and topical corticosteroids, additionally to adjuvant treatment for pruritus [15]. Second-line therapies composed of phototherapy and systemic immunomodulators. Besides, oral antihistamines and systemic antibiotics also play a crucial role in the management of atopic dermatitis [16]. At present, biologics and targeted disease-modifying therapies were developed to provide an effective control for adult with moderate-to-severe AD [17]. In Vietnam, the Ministry of Health has released the guideline for diagnosis and treatment of dermatological diseases, including AD [18]. Based on the guideline, the combing therapies have been used for the patients depending on their AD characteristics. However, the more data evaluating effects of the combing therapeutic methods based on the guidelines are still required.

In this regard, we conducted the study to evaluate the effects of combining therapies on the Vietnamese inpatients with AD. First, we investigated clinical features, stages, severity levels of Vietnamese patients with AD, and then measured the treatment results by combining therapies in those patients. We hypothesized that the combination of therapeutic methods based on the Vietnamese dermatology practice guidelines might improve symptoms in patients with AD.

Materials and Methods

Study design

This cross-sectional study was conducted between May 2018 and May 2020. The procedure of this study was approved by the Scientific and Ethical Research Council of Can Tho University of Medicine and Pharmacy with the decision number being 010/PCT-HDDD. The steps were followed ethical criteria in medical research: The research participants are explained specifically and clearly about the purpose, the use of the results, and the research process.

Participants

Adult patients with AD were followed and treated at the Inpatient Department of Can Tho Dermato-Venereology Hospital. Qualified patients who met the inclusion criteria and exclusion criteria were enrolled in our study. Inclusion criteria include as follow: (1) Patients were diagnosed with AD based on the standard of Hanifin and Rajka in 1980 [5], and (2) ≥12-years-old (we defined adult AD as AD patients with an onset age older than 12 years 8, [19]). Exclusion criteria included the followings: (1) Patients have skin disorders in the same location, (2) patients having signs of severe heart, liver, kidney, or lung failure, (3) patients have immunodeficiency such as HIV/AIDS and diabetes, and (4) patients having symptoms which were side effects of corticosteroids such as skin atrophy, vasodilation and/or hirsutism.

In our cross-sectional study, the aim was to estimate the prevalence of severity level of adult AD patients or finding the average value of some quantitative variable in a population. Therefore, the sample size was calculated based on the estimating proportion formula $(n = \frac{Z^2_{1-\frac{\alpha}{2}} \cdot p(1-p)}{d^2})$ [20].

So that the sample size (n) might be smallest. This estimation was based on considering a confidence level of 95% (α = 5%), d is a margin of error of 6%, the critical value is $Z_{1-\frac{\alpha}{2}}$ 1.96, choosing the sample proportion (p) is 0.861 because according to Van *et al.* the ratio of moderate to severe level in patients with atopic dermatitis was 86.1% [18]. Therefore, the sample size (n) based on the above formula was 128 patients. Data were prospectively collected to demonstrate demographics (age, sex, ethnicity, and occupation), AD individual and family history, clinical features, such as: Age of onset, disease duration, lesion characteristics, comorbidities, AD stage, and severity level.

Intervention

Regarding disease management and treatment, data on prescribed AD treatments were collected. According to the guidelines for diagnosis and treatment of dermatological diseases of the Vietnam Ministry of Health, the protocol of treatment includes topical and systemic treatments [18]. The topical treatments depended on stage of the disease (acute, subacute, or chronic stage). About the systemic treatments included antihistamines, oral corticosteroids, antibiotics, and others such as Vitamin AD and Vitamin E.

AD severity was based on the SCORAD index (mild: SCORAD <25, moderate: 25–50, and severe: >50). Clinical symptoms and SCORAD scores were regularly monitored at the time of admission, 3 days, 7 days, and 14 days of treatments. The treatment results were assessed through the improvement of clinical presentation and the SCORAD index. Concretely, patients were divided into three groups including good response (improving clinical presentations, decreasing total SCORAD, and decreasing severity level), average response (improving clinical presentations, decreasing total SCORAD, and but not decreasing severity level), and non-/poor response (not improving clinical presentations and not decreasing total SCORAD, even might increasing total SCORAD). Besides, our study also recorded the unwanted effects of therapies.

Statistical analysis

All data of patients were input into the Statistical Package for the Social Sciences software version 20.0 for statistical analysis. Qualitative variables were described by frequency and percentage. For continuous variables, the mean ± standard deviation (SD) was used to illustrate the data distribution. One-Sample Kolmogorov–Smirnov test was used to test the normality of the data distribution of quantitative variables. Chi-square tests were used to describe the relationship between two qualitative variables. Independent sample t-test was used to compare the mean of two independent groups. The one-way ANOVA test compared the mean of multiple groups. Paired sample t-test compared the mean at two time points of a group. Statistical parameters are presented with 95% confidence intervals, $p < 0.05$ was considered as a significant difference level.

Results

Participants' characteristics

A total of 128 adult patients were diagnosed with atopic dermatitis based on the Rajka and Hanifi diagnostic standards. The mean age of adult ad was 53.34 ± 22.19 years, and the highest proportion was the above 60-year-old group, accounting for 45.3% (n = 58). The average age for disease onset age was 48.41 ± 21.32 years. While 12.5% (n = 16) of ad patients had the disease beginning before mature age, 87.5% (n = 112) had the onset of the disease after 18-years-old, thus that a late-onset ad is much more popular. In addition, males made up a bigger percentage of adult AD patients when compared to females (64% vs. 36%) (Table 1).

Table 1: Demographic characteristics

Patient characteristics	Value
Patient number	128
Gender (male/female)	82/46
Age	53.34 ± 22.19 (from 12 to 90 year old)
Onset age	48.41 ± 21.32 (from 2 to 84)
Disease duration (years), median (Q1–Q3)	3 (2–7)

Clinical characteristics

About the stage and the severity of adult ad patients, sub-acute phase was the highest percentage at 57.8%, followed by acute phase 28.9%, and chronic phase 10.16%. Average SCORAD score was 48.53 ± 8.5. In addition, moderate and severe consisted of a similar proportion at 48.8%, and the lowest rate was mild at 27.34% (Table 2).

Pruritus was the most common symptom in all patients (100%). About personal history, enjoying the highest proportion was the personal history of atopic dermatitis, accounting for 96.1%. When analyzing the association between severity of AD with personal AD history, we recorded that the proportion of severe and moderate level were higher than mild level (50.4% and 47.2% vs. 2.4%, p = 0.024), suggesting that the history of personal could have the relation with the level disease of adult AD patients (Table 3).

Table 2: Stage and level of the disease

Stage and level of the disease	*n* (%)
Stage of disease	
Acute	37 (28.9)
Subacute	74 (57.8)
Chronic	17 (13.3)
Level of disease (based on SCORAD)	
Mild	4 (3.1)
Moderate	62 (48.8)
Severe	62 (48.8)
SCORAD (mean ± SD)	48.53 ± 8.5

SCORAD: SCORing Atopic Dermatitis, SD: Standard deviation.

Table 3: Main symptoms

Main symptoms	***n*** (%)
Pruritus	128 (100)
Skin lesions with typical morphology and location	126 (98.4)
Chronic recurrent or chronic dermatitis	127 (99.2)
History of personal	
Asthma	2 (1.6)
Allergic rhinitis	14 (10.9)
Atopic dermatitis	123 (96.1)
History of family	
Asthma	7 (5.5)
Allergic rhinitis	23 (18)
Atopic dermatitis	3 (2.3)

Regarding minor symptoms, xerosis accounted the highest position at 72.7% (n = 93) while the lowest proportion was Dennie-Morgan infraorbital fold symptom (1.6%, n = 2). We also analyzed the relation of xerosis symptom, and the level of disease and the results showed that the most common level disease in AD patients was severe level (59.1%), followed by moderate level (39.8%), and mild level (1.1%). Thus, xerosis could affect the severity of the disease ($p = 2 \times 10^{-5}$) (Table 4).

Table 4: Minor symptoms

Minor symptoms	*n* (%)
Xerosis	93 (72.7)
Ichthyosis/palmar hyperlinearity, keratosis pilaris	35 (27.3)
Early age of onset	9 (7)
Tendency toward cutaneous infections	87 (68)
Tendency toward nonspecific hand or foot dermatitis	71 (55.5)
Eczematous cheilitis	7 (5.5)
Dennie-Morgan infraorbital fold	2 (1.6)
Orbital darkening	4 (3.1)
Pityriasis alba	62 (48.4)
Anterior neck folds	22 (17.2)
Itching when sweating	87 (68)
Intolerance to wool ad lipid solvents	63 (49.2)
Keratoconus	30 (23.4)
Food allergy	88 (68.8)
Disease progression can be affected by environmental and mental factors	83 (64.8)
White dermographism delayed blanch	6 (4.7)

The results of treatment by combining therapy

Most patients received systemic and/or topical pharmacological therapy. Topical treatments were prescribed for 125 (96.1%) patients, systemic treatments for 112 (86.1%), and 125 (96.1%) patients were simultaneously taking more than one treatment during the study. We evaluated the treatment results

in adult atopic dermatitis patients after 3 days, 7 days, and 14 days based on the change in SCORAD score and the improvement of disease level. After 2 weeks of treatments, the assessment of the clinical response in SCORAD showed good response in 88.4% (n = 108) patients, average improvement in 15.6% (n = 20) patients, and no patients with non-/poor improvement. Dramatic improvements in the SCORAD score were detected in adult AD patients after treatment. After 14 days, 38 patients (29.7%) were classified as having moderate disease, 90 (70.3%) were classified as having mild disease, and no patient was classified as having severe disease (Figures 1 and 2).

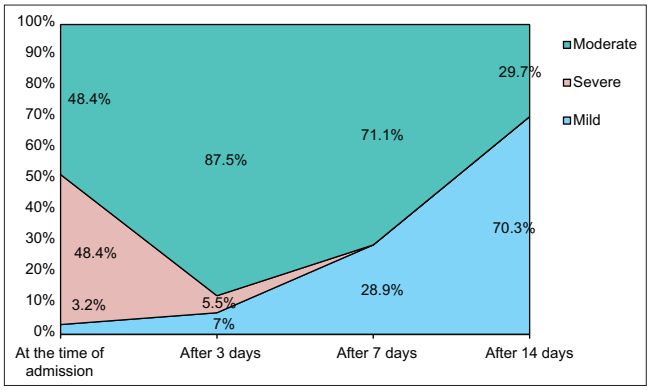

Figure 1: Distribution of the percentages of patients with adult atopic dermatitis according to disease level after 3, 7, and 14 days of treatments

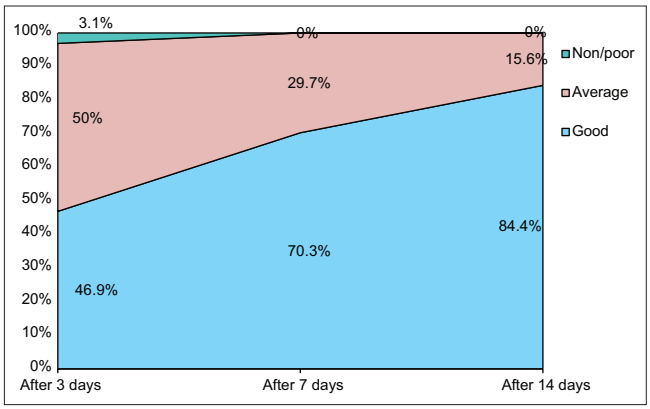

Figure 2. Distribution of the percentages of patients with adult atopic dermatitis according to response level after 3, 7, and 14 days of treatments

After 3 days of treatments, the mean SCORAD index slightly decreased by 9.07 points (18.77%), from 48.3 to 39.23 points ($p = 6.1 \times 10^{-43}$). Subsequently, after 7 days treatments, the mean was 27.6 ± 5.12 points and this number gradually declined by 42.86% (20.7 points, $p = 3.1 \times 10^{-61}$). Most patients achieved a 50% improvement, with 70.3% of patients showing a good response and 29.7% presenting an average response. Furthermore, after 14 days of treatments, the mean of SCORAD had a significant fall from 48.3 to 23.86 points (50.56%, 24.43 points), with a statistically significant difference before and after treatment ($p = 4.7 \times 10^{-65}$) (Figure 3). During our survey, after the follow-up period of 3, 7, and 14 days, we recorded 16 patients (12.3%) had undesirable effects due to the system treatments, most were side effects of oral corticosteroids caused on the digestive system. There was 0% unwanted effects due to topical treatments.

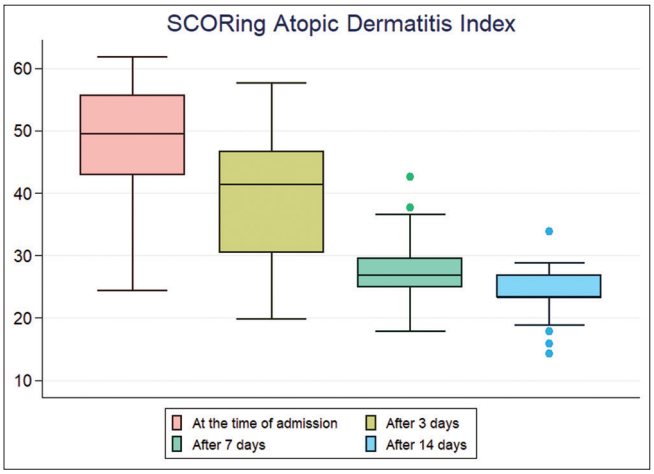

Figure 3: Distribution of the mean SCORAD index after 3, 7, and 14 days of treatments

Discussion

The present study aimed to demonstrate the clinical profile and evaluate the treatment results of the combination therapies based on the Vietnamese dermatology practice guidelines in adults with AD. Our results revealed that: (1) The late-onset AD constituted the largest proportion of total researched patients. (2) The moderate-to-serve group made up the dominant percentage of the adult AD hospitalization patients. (3) Pruritus was the most common symptom in all patients. (4) There was a correlation between xerosis symptom and disease severity. (5) The combinations of pharmacological therapies had significant effectiveness and relative safety in treatment of adult AD inpatients in the first 2 weeks. Our study supports that the combinations of therapies were the good options in AD patients with the late-onset AD, who regularly had pruritus and xerosis symptoms, in the initial managements of adult AD patients.

Our study recorded that 87.5% of Vietnamese patients developed the condition after 18 years old. Similarly, a previous study conducted on China population showed that 59.7% of patients had adult AD and the onset age was 35 years or so [8]. Another study observed that the average age at AD diagnosis of Europeans and Americans was 31 years [21]. These findings suggested that AD might be mainly late-onset. The reason for this phenomenon is because of the rapid economic development, which has resulted in a significant change in manufacturing methods and living habits as well as increased concern about environmental issues [22]. While the pathogenesis of

AD is linked to genetic factors, environmental factors such as air pollution and aeroallergens (e.g., pet hair, house dust mite, and pollen) may give rise to the growth of the incidence rate. Furthermore, stratum corneum wall could be damaged by altering lifestyles including frequently utilizing soap or staying a long time in air-conditioned room [23]. Thus, the average age of beginning of AD disease is increasing.

The current study showed that most adult patients with AD had the moderate-to-serve level (at 97.6%). Supportively, a recent study found that the proportion of the moderate-to-serve level AD patients made up 72.65% [19]. Another study conducting in Brazil population showed that there were 83.1% AD patients classified as the moderate-to-serve group [24]. This was similar to the recent treatment of the European and Japan Guidelines, patients who were assessed as mild are often consulted for outpatient treatment while patients that required hospitalization due to AD mainly of moderate and severe severity [25], [26].

Itch is a major characteristic in the diagnostic criteria and a hallmark of AD [27]. Moreover, pruritus is the predominant symptom of AD and it occurs in most patients at different stages [28]. In our study, all adult AD patients had itchy symptoms, which is consistent other studies [19], [24]. The itch-scratch phenomenon in atopic dermatitis is a mechanism that makes itching symptoms prolonged and difficult to control [27]. In addition, not only could this symptom affect in both daily activities and patients' sleep, but this also reflected the severity of AD [29]. Thus, managing pruritus played an essential role in the treatment of AD.

Our study also reported that the xerosis symptom in the moderate-to-sever group accounted for a higher percentage (72.7%). It was possibly due to decreased ceramide levels and filaggrin defects, which resulted in heightened transepidermal water loss [30]. An author of an atopic dermatitis study also observed a high rate of dry skin at 78.91% [19]. In addition, we recoded that dry skin was associated with the severity in AD patients ($p < 0.0001$). Furthermore, a previous study has suggested that xerosis was positively related with AD in an adult general population (at 47.5%, $p = 2 \times 10^{-5}$) [30]. Thence, suggesting that managing xerosis may support preventing the development of flares and the severity of AD.

We identified that the assessment of the clinical response in SCORAD showed a good response in 88.4% of patients after 2 weeks of treatments. The mean of SCORAD declined considerably from 48.3 to 23.86 points (50.56 %, different −24.43 points from baseline), with a statistically significant difference before and after treatment ($p = 4.7 \times 10^{-65}$, Paired-Sample t-test). In our study, the main topical therapies included bathing with 1/10000 KMnO4 (96.1%), moisturizer cream (42.2%), and topical corticosteroid (33.6%). The above methods had the effect of soothing the skin, antibacterial, cleaning the scales, and softening the skin [31]. Besides, it was important to encourage patients to use moisturizing ointments to maintain efficacy in treatment and prevent recurrence of AD [31].

Regarding the systemic medications, in a recent study, investigators have reported that AD patients treated with systemic antibiotics showed a marked reduction in disease progression. Systemic antibiotics have been shown to improve disease progression. Of the antibiotic classes, cephalosporins were shown to be the best, significantly improving skin infections [11], [19]. In addition, the authors of other studies have also reported that systemic corticosteroids should be the most frequently used in adult AD patients to induce remission and relieve symptoms in severe cases in the short term [31]. Supportively, a study had shown that the combination therapy including oral antibiotics and topical corticosteroids also had a dramatically higher rate of *S. aureus* excretion at the end of treatment [19]. Moreover, the mean SCORAD scores also declined to 16.61 ± 3.85 (difference in −−28 points from admission) after 2 weeks of treatments [19]. Hence, we suggested that the combining therapies significantly improved symptoms and severity in patients with AD.

Study's limitation

In our study's findings, there are several limitations that should be addressed. First, our research only illustrated on adults, although it had epidemiological significance, it was not highly representative. Second, most of the treatment was based on the physician's experience and the patient's clinical course, so we were unable to draw any conclusions regarding the specific combining therapies. Finally, because the duration of follow-up treatment was brief (14 days), it was hard to assess the treatment's long-term effectiveness and evaluate the relapsed conditions.

Conclusion and Perspective

Our findings demonstrated that adult atopic dermatitis patients are often hospitalized in the subacute stage and moderate-to-severe level. Pruritus is the main and most common symptom in adults with AD, so proper treatment should be involved to reduce discomfort in patient's lives and limit the superinfection caused by pruritus. The percentage of patients who had xerosis was 73.1%, so moisturizers remained a fundamental part of the management of AD. In addition, the SCORAD score improves significantly after 3, 7, and 14 days of the combination of therapeutic methods. Therefore, combination treatment therapies are extremely necessary for the effective treatment of adult AD patients. Finally, evaluating the long-term effectiveness of treatment and the problem of

recurrence in adult patients with AD need to be made clear in further studies.

Authors' Contributions

NTTT and HVB contributed to the conceptualization, NTTT and HVB contributed to the methodology, NTTT and HVB contributed to the collection, synthesis, and interpretation of data. TNAT and HND drafted the manuscript. TNAT, NTTT, HND, and HVB edited and revised the manuscript. All authors approved the final version of the manuscript.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Can Tho University of Medicine and Pharmacy (protocol code: 010/PCT-HDDD and date of approval: 15/5/2018).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, Huynh Van Ba, on reasonable request.

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