



ORIGINAL ARTICLE

Alitretinoin Compliance in Patients with Chronic Hand Eczema

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Background: Oral alitretinoin is effective in the treatment of chronic hand eczema (CHE), and ≥ 12 weeks of alitretinoin treatment has been shown to be effective in Korean patients. However, in the real world, a considerable number of patients discontinue alitretinoin, which leads to treatment failure. **Objective:** To evaluate the compliance rate of alitretinoin treatment and explore common reasons for poor compliance in patients with CHE in the real world. **Methods:** We retrospectively reviewed the electronic medical records of CHE patients treated with alitretinoin. We defined 'poor-compliance' as subjects who were treated with alitretinoin for < 12 weeks and 'good-compliance' as subjects who were treated with alitretinoin for ≥ 12 weeks. We reviewed the demographics, dose, and duration of alitretinoin usage, efficacy, and reasons for poor compliance. **Results:** A total of 137 subjects were enrolled, and 77 (56.2%) did not complete the 12-week treatment with alitretinoin. Among them, the non-improvement rate was significantly higher in the poor-compliance group than in the good-compliance group ($p < 0.01$). The main reasons for the alitretinoin cessation in the poor-compliance group were insufficient response (40.8%), followed by high cost (34.7%), and adverse events

(24.5%). **Conclusion:** Alitretinoin appears the preferred long-term treatment option for CHE. Although there are complaints about late efficacy, cost, and side effects, following proper explanation, these should not justify discontinuation. Physicians need to recognize the reasons for poor compliance with alitretinoin for each patient and suggest continuing alitretinoin for the successful treatment of CHE. (*Ann Dermatol* 33(1) 46 ~ 51, 2021)

-Keywords-

Alitretinoin, Compliance, Eczema, Hand

INTRODUCTION

Hand eczema (HE) is the most widely recognized form of dermatitis to influence the hands¹. Chronic hand eczema (CHE) is a chronic form of HE that persists for more than 3 months or recurs more than twice within a year¹. Approximately 10% of CHE patients are diagnosed with severe CHE by the Physician Global Assessment (PGA), and their long-term prognosis is poor¹. The reliable use of emollients, topical or systemic steroids, and avoiding aggravating factors can be options for treating mild cases of CHE. However, these conventional treatments yield unsatisfactory results in severe CHE²⁻⁴.

Alitretinoin (9-*cis* isomer of retinoic acid) is a vitamin A metabolite that has been used as a topical or systemic medicine for severe acne vulgaris, psoriasis, and certain malignancies⁵. Alitretinoin is the first drug to be approved as a treatment option for CHE that is unresponsive to classical topical steroids⁶. In clinical trials, studies have shown that alitretinoin for up to 24 weeks is highly effective with a good safety profile⁵. Furthermore, adherence to daily treat-

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ment with alitretinoin for 12 weeks or more was found to be effective in treating CHE in Korean patients¹. However, poor compliance with alitretinoin remains a primary cause of treatment failure and is a major challenge that dermatologists encounter in managing CHE patients³. There are limited studies on the alitretinoin compliance in CHE, and our retrospective study aimed to evaluate the compliance of alitretinoin and reasons for poor compliance in the real world.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board (IRB) of the Inje University Busan Paik Hospital (IRB No. 18-0184).

Study subjects

We performed a retrospective chart review of 137 CHE patients who were prescribed with 10 or 30 mg of alitretinoin at the Busan Paik Hospital and Haeundae Paik Hospital Dermatology Clinic between 2013 and 2018. Patients were included if the following criteria were met: (1) disease duration of at least 3 months or more than two flares within the last 12 months with moderate to severe CHE defined according to the PGA score⁶; (2) pretreatment with topical corticosteroids and no long-lasting healing under adequate topical treatment; and (3) no allergic contact eczema of the hand, psoriasis, atopic dermatitis, or acute skin infections dominating the clinical picture.

Data collection and analysis

Fig. 1 shows the classification flow. We defined the 'poor-compliance group' as subjects who were administered with alitretinoin medication for less than 12 weeks with (improved PGA score) or without clinical improvement (similar or

worsened PGA score), whereas the 'good-compliance group' comprised subjects who were administered with alitretinoin medication for more than 12 weeks.

Based on the classification, we reviewed the electronic medical records of patients, including demographics (sex, age), dose and duration of alitretinoin usage, efficacy of alitretinoin, reasons for poor compliance, and laboratory test results.

Efficacy and compliance assessments

Efficacy was evaluated by the PGA score at the time patients stopped the alitretinoin treatment. We compared the difference between patients who were treated for less than 12 weeks and those for 12 weeks or more. Regarding the patients in the 'poor-compliance' group, we collected their reasons for alitretinoin withdrawal and analyzed specific adverse drug reactions (ADRs). Furthermore, we subdivided the patients by sex, age, and treatment duration to compare compliance and efficacy.

Statistical analysis

All data were calculated using IBM SPSS (IBM SPSS Statistics 23.0; IBM Corp., Armonk, NY, USA), and the mean values were identified. The Pearson's chi-squared test and independent two-sample t-test were used for statistical analysis. Results were considered statistically significant at a *p*-value of less than 0.05.

RESULTS

Demographic information

A total of 137 moderate (*n* = 31; 22.6%) to severe (*n* = 106; 77.4%) CHE patients were included in this study, and the overall demographic information and alitretinoin usage is shown in Table 1. There was a female predominance, and more than half of the patients were in their 30s~50s. A

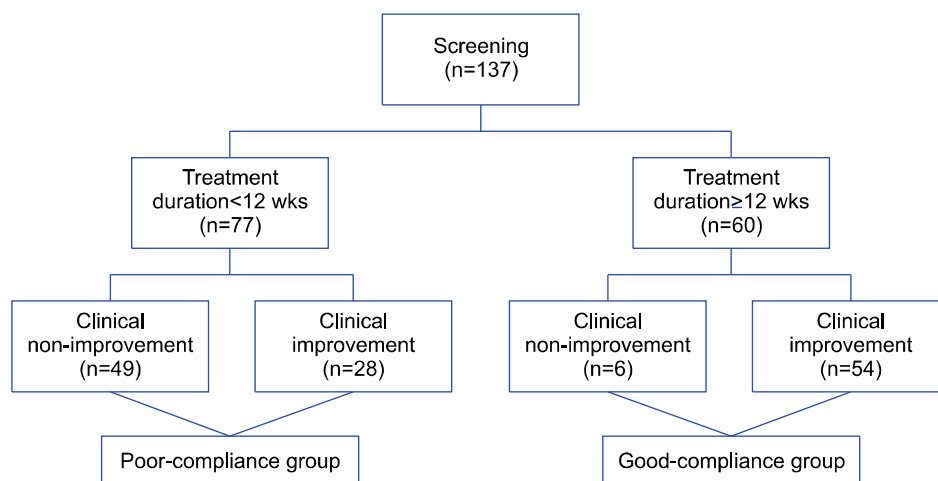


Fig. 1. Flow of study participants.

total of 60 patients (43.8%) were treated for more than 12 weeks (good-compliance group) and 77 (56.2%) were treated for less than 12 weeks (poor-compliance group); among them, 49 were treated for less than 12 weeks without clinical improvement.

Clinical improvement according to treatment duration and alitretinoin dosage

Clinical improvement was significantly higher when CHE

Table 1. Demographic informations

Variable	Number (%)
Sex	
Male	57 (41.6)
Female	80 (58.4)
Age (yr)	
≤ 29	21 (15.3)
30 ~ 39	21 (15.3)
40 ~ 49	29 (21.2)
50 ~ 59	36 (26.3)
60 ~ 69	20 (14.6)
≥ 70	10 (7.3)
PGA score	
Moderate	31 (22.6)
Severe	106 (77.4)
Treatment duration (wk)	
< 4	51 (37.2)
≥ 4 ~ < 8	19 (13.9)
≥ 8 ~ < 12	7 (5.1)
≥ 12	60 (43.8)
Alitretinoin dose	
10 mg	10 (7.3)
30 mg	127 (92.7)
Efficacy	
Improvement	82 (59.9)
Non-improvement	55 (40.1)

PGA: Physician Global Assessment.

was treated with alitretinoin for more than 12 weeks ($p < 0.01$). A dose of 30 mg of alitretinoin had higher rate of clinical improvement than 10 mg of alitretinoin, although they were not significant ($p = 0.509$; Fig. 2). A total of 28 patients who improved within 12 weeks had a 1.04-point improvement in their PGA scores, and 54 patients who improved after 12 weeks had a one-point improvement in their PGA scores.

Relationship between compliance and sex, age, alitretinoin, and duration

When we compared the good-compliance and poor-compliance groups, people aged 50 ~ 59 years were more likely to be included in the good-compliance group, but there was no statistical significance ($p > 0.05$). Furthermore, 30 mg of alitretinoin had higher compliance rate ($n = 46$, 36.2%) than 10 mg of alitretinoin ($n = 3$, 33.3%), but there

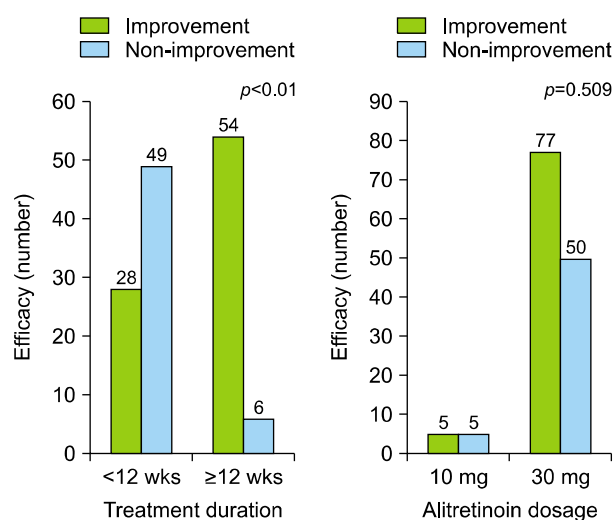


Fig. 2. Relativity between treatment duration, alitretinoin dosage and efficacy of chronic hand eczema.

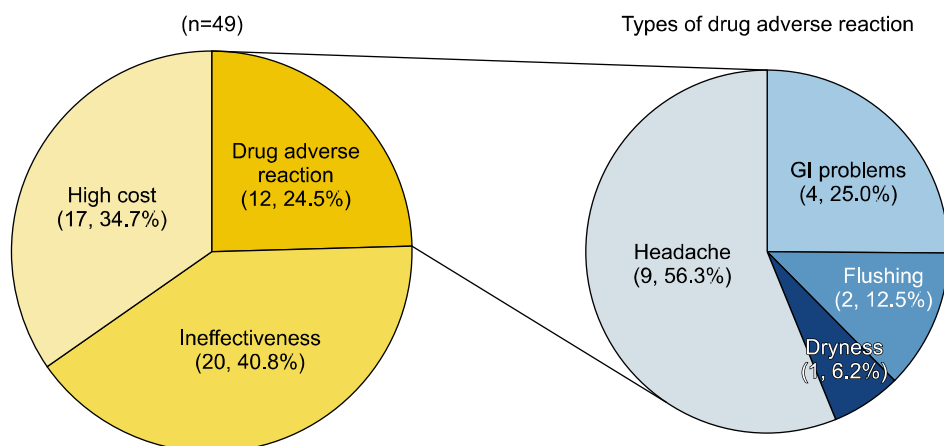


Fig. 3. The reason of poor-compliance in patients without clinical improvement. GI: gastrointestinal.

was no statistical significance ($p > 0.05$). In terms of alitretinoin dosage, the good-compliance group was occupied more than the poor-compliance group regardless of dose. In the poor-compliance group, 51 of the 77 patients stopped treatment with alitretinoin within 4 weeks.

Reasons for poor compliance

Among the 77 patients in the poor-compliance group, 28 (36.4%) showed clinical improvement and 49 (63.6%) did not.

1) Patients with clinical improvement (n = 28)

A total of 28 patients with clinical improvement of CHE stopped alitretinoin within 12 weeks. Their PGA score decreased from 4.85 to 3.82, showing a decrease of approximately one point. Five of the 28 patients showed relapse after a 4-month average.

2) Patients without clinical improvement (n = 49)

The primary reason for alitretinoin stoppage in the poor-compliance group without clinical improvement was ineffectiveness ($n = 20$, 40.8%), followed by high cost ($n = 17$, 34.7%), and ADRs ($n = 12$, 24.5%) (Fig. 3). Ineffectiveness was the main reason for stoppage in male patients, while high cost was the main reason for stoppage in female patients. Patients aged over 60 years who had used alitretinoin for 4 to 8 weeks most often discontinued the use due to ineffectiveness. At the age of 40, the high cost was the most likely reason for the alitretinoin stoppage. The reasons for patients discontinuing alitretinoin before 4 weeks were ineffectiveness and high cost in equal numbers.

Drug adverse reactions

Among all patients with ongoing alitretinoin treatment, 54 (39.4%) complained of ADRs, none of which were fatal (headache, 28; gastrointestinal [GI] problems, 6; flushing, 3; arthralgia, 1; dizziness, 1; dryness, 1; general weakness, 1); of the 54 patients, 13 had laboratory abnormalities. The occurrence of headache was not associated with alitretinoin dose ($p = 0.460$). Patients who used alitretinoin for less than 12 weeks had higher ADR rates, but this was not significant ($p = 0.135$). In addition, the proportion of patients showing clinical improvement was significantly higher if alitretinoin was continued for over 12 weeks. The laboratory test results were not shown because they were only performed on 35 patients, and 13 patients showed mild abnormal lipid profile and thyroid function that did not affect the compliance, dosage modification, and duration of alitretinoin treatment.

DISCUSSION

CHE is a chronic form of HE that persists for more than 3 months or recurs for more than twice within a year^{1,7,8}. Genetic predisposition, altered immune response, and environmental factors, such as handling chemicals or other skin irritants, have all been suggested as contributing factors for CHE. Pain, itching, and bleeding from fissures can make manual tasks challenging to perform, and embarrassment caused by persistent disfigurement of the hand may cause substantial physical, social, and psychological stress^{2,3}. Moreover, CHE may cause an economic burden and decrease the quality of life of patients. Although mild cases of CHE can be managed by avoiding irritants and/or using emollients with topical corticosteroids, severe CHE is extremely challenging to manage and represents a considerable unmet medical need⁴.

Alitretinoin (9-*cis* isomer of retinoic acid), a vitamin A metabolite, has pharmacological effects on cell proliferation, differentiation, apoptosis, angiogenesis, keratinization, sebum secretion, and immunomodulation mediated by nuclear retinoic acid receptors and retinoid X receptors⁵. Alitretinoin suppresses chemokines that are involved in the recruitment of leukocytes to the sites of skin inflammation, expansion of T lymphocytes, and antigen-presenting cells mediating inflammatory responses and suppressing allo-genic leukocyte activation^{9,10}. Alitretinoin is the first drug to be approved as a treatment option for CHE that is unresponsive to classical topical steroids^{5,6,9,11}. In clinical trials, including the BACH trial (randomized double-blind placebo-controlled study), TOCCATA open study (non-interventional study), and meta-analysis, studies have shown that alitretinoin treatment for up to 24 weeks is a highly effective medicine with a good safety profile^{3,5,8,12}. Furthermore, Kwon et al.¹ reported that daily use of alitretinoin for 12 weeks was effective in treating Korean patients with CHE.

In our study, 137 patients with CHE using alitretinoin were analyzed, and there were a greater number of females and males in their 40s and 50s. The difference in age distribution between the current study and the previous studies may be because our study design only included patients with moderate to severe CHE. In addition, younger patients with CHE would not have been included because they tend to avoid treatment with alitretinoin because of its relatively high cost and possibility of fetal malformations. When treated for more than 12 weeks, the efficacy of alitretinoin was significant in our study, which was higher than the previous Korean study (90% vs. 44.4%)¹. It may be because, in our study, all patients who showed improvement of the PGA score were included; however,

in the previous study, the improvement was achieved only after 'clear' or 'almost clear'. Although alitretinoin showed good efficacy, more than half of the patients did not complete a sufficient treatment period for alitretinoin, indicating that poor compliance is a major reason for treatment failure rather than the efficacy of the drug itself. In a previous Korean study, the compliance rate was 70.3%, which was higher than ours¹. It is presumed that previous prospective studies that looked at efficacy and safety might have attempted to improve patient compliance. Similarly, in terms of dosage, 30 mg of alitretinoin is much more effective than 10 mg. In addition, 10 mg of alitretinoin is known to be used if there are side effects or when underlying diseases, such as diabetes and cardiovascular disease, are present. However, the difference between 30 mg and 10 mg in our study was not significant, although the former was more effective. It may be because the 10 mg was used by a female patient with low weight or patients with kidney dysfunction. Furthermore, there were only 10 (7.3%) patients who used 10 mg of alitretinoin. Moreover, more patients used sufficient period in their 30 mg of alitretinoin, which is presumed to be used for a long time because it seemed that 30 mg was more effective for the patients.

When the reasons for alitretinoin discontinuation in the poor-compliance group were analyzed, all 28 patients with clinical improvement discontinued alitretinoin as soon as they showed improvement. Of them, five relapsed after an average of 4 months, which was shorter than the 6 months reported in previous studies¹¹. This may be because our patients underwent follow-up assessment at shorter intervals. Patients without clinical improvement stopped alitretinoin for various reasons, but majority discontinued treatment because they felt that it was ineffective. Most of the patients who were dissatisfied stopped alitretinoin within 4 weeks, a much shorter period than the recommended dose duration. Alitretinoin is known to require a sufficient dose duration to show its maximal effect, which corresponds to the results of the current study as well as to those of previous studies. The reason a large proportion of patients ceased taking alitretinoin early seems to be due to insufficient explanation from dermatologists. In addition, patients had a low level of understanding that they should take alitretinoin for a sufficient amount of time. Korean patients with urgent personality characteristics who expect fast improvement may also be likely to discontinue medication earlier¹³. Furthermore, in the analysis of patients in the poor-compliance group who stopped alitretinoin within 4 weeks, the number of patients who stopped because of high cost was the same as the number of patients who stopped because they believed the treatment was ineffec-

tive. In Korea, alitretinoin (Alitoc[®]; GlaxoSmithKline (GSK), Brentford, England) tends to be more expensive with regards to insurance coverage than classical CHE treatments. A study of cost-effectiveness concerning CHE patients in Switzerland, which estimated the incremental cost-effectiveness ratio and clinical effectiveness (quality-adjusted life years [QALYs] derived from a randomized controlled clinical trial) in patients with severe CHE showed the cost-effectiveness of oral alitretinoin². This study concluded that although alitretinoin costs more in total treatment costs (€42,208) than in supportive therapy (€38,795), the QALYs were higher in the alitretinoin group (11.21 vs. 10.98), and it was cost-effective in comparison with existing cost-effectiveness thresholds².

Many clinical trials, including the BACH trial and TOCCATA open study, have shown the effectiveness of alitretinoin over a course of 24 weeks, while Gulliver and Baker¹⁴ reported effective treatment of CHE with 36 continuous months of alitretinoin treatment. Considering that moderate to severe CHE tends to be refractory to conventional therapy, there are few alternatives to alitretinoin. Thus, it is necessary to persuade patients that alitretinoin should not be discontinued simply due to ineffectiveness or high cost.

Some patients stop alitretinoin due to ADRs, which are irritating symptoms such as headache, GI problems, flushing, and dryness. Laboratory abnormalities may be asymptomatic and only detected by examination by a physician; therefore, laboratory abnormalities may not be a factor in lowering compliance. In our study, headache was the most common side effect, as in other studies, and tends to diminish with the continuous use of alitretinoin^{1,5}. In addition, like other side effects, such as GI problems, flushing, and dryness, a dose reduction or symptomatic care can manage symptoms. Serious ADRs, such as myocardial infarction, lymphatic edema, paranoia, rectosigmoiditis, and soft tissue swelling, have rarely been reported and are related to underlying diseases and not associated with alitretinoin use¹¹. Chronic alitretinoin administration for up to 24 weeks did not lead to drug accumulation in the body, which verifies its long-term safety¹⁵. That is, most ADRs of alitretinoin are predictable and manageable. Therefore, improved patient screening, education for patients, and close attention to follow-up, for example through telephone and message reminders, may be critical in increasing compliance.

The subjects included in this study were moderate to severe CHE patients who had failed conventional treatments. In this study, several factors, such as ineffectiveness, high cost, and ADRs were revealed to result in lower compliance; however, most of these factors are not reasons to

discontinue alitretinoin from a doctor's perspective. Considering pharmacological characteristics and other treatment modalities, dermatologists should explain the factors that reduce compliance before initiating treatment. In addition, detailed counselling and management of the factors affecting compliance should be provided at every visit to raise the alitretinoin compliance.

The retrospective nature of our study limited our ability to collect case-controlled data. Furthermore, this review was conducted with a relatively small number of patients (n = 137) in only two centers. In the future, a large customized study is needed for better analysis of compliance with alitretinoin.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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