Efficacy and Safety of Treatment with Oral Alitretinoin and Oral Cyclosporine for Chronic Hand Eczema: A Retrospective Review of 118 Cases

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Mild hand eczema is generally treated with emollients or topical steroids, and patients are recommended to avoid irritants. If conventional treatment is not effective, systemic treatment can be used. Alitretinoin is approved for the treatment of chronic hand eczema in patients who are unresponsive to potent topical steroids (1). Cyclosporine, a systemic remedy that has recently attracted attention, has been demonstrated to be effective in treating severe relapsing chronic hand eczema (2–4). A recent study reported similarities between histopathological findings from chronic hand eczema and psoriasis located on the hands (5). This suggests that cyclosporine, which is commonly used for psoriasis treatment may be a treatment option for chronic hand eczema.

The aim of this study is to compare the efficacy and safety of alitretinoin and cyclosporine treatment in the context of chronic hand eczema and to provide information that can be helpful to patients with chronic hand eczema who are unresponsive to treatment.

PATIENTS, METHODS AND RESULTS

Among the 118 patients who visited the Department of Dermatology, Hallym University Sacred Heart Hospital, Anyang, Korea, between January 2010 and December 2018, those with chronic hand eczema who did not respond to topical steroid treatment for more than 4 weeks and who used oral alitretinoin or oral cyclosporine were reviewed. Patients treated with alitretinoin, cyclosporine or other systemic treatments in the previous 3 months were excluded. Patients with predominantly atopic dermatitis, in whom the hands are also involved, were also excluded. This study was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital, and the requirement for informed consent was waived (IRB no, 2018–I007).

All 53 alitretinoin-treated patients began treatment with oral alitretinoin, administered as a 30 mg capsule once daily. Of the patients receiving cyclosporine treatment, 65 began with a daily dose of 3~5mg/kg/day (split into 2 doses) of cyclosporine capsules. In addition, emollients and topical steroids were used continuously as usual. Adequate dose reductions were made in both groups whenever significant adverse events occurred.

We retrospectively analysed electronic medical records (EMR) related to patient characteristics, history of atopic dermatitis, underlying disease, subtypes of hand eczema (6), adverse events, laboratory parameters, co-medication, treatment duration, and concomitant use of topical corticosteroids. Disease severity was evaluated using Physician's Global Assessment (PGA) score. Based on an effectuated photo-guide developed by Coenraads et al. (7), the PGA characterizes the severity of the 5 stages (clear, almost clear, moderate, severe, very severe) and takes into account the relative hand surface ratio involved and the intensity of clinical symptoms. All participants took a clinical photograph at each outpatient visit. The severity of hand eczema was evaluated by 3 clinicians who performed a detailed study of the clinical photographs.

The clinical efficacy was recorded according to the PGA score obtained at week 24. The reasons for early cessation of treatment were also recorded, and these reasons were subdivided as ineffectiveness, adverse events, disease control, other cessation reason, and lost to follow-up. When the patient reached "clear" or "almost clear," they were considered responsive to treatment. Adverse events associated with the use of each drug were reviewed through EMR.

Statistical analysis was performed using SPSS version 24.0 for Windows (Statistical Package for the Social Sciences, SPSS, Chicago, IL, USA). All parameters were presented descriptively, and for continuous variables, the descriptive parameters included number, mean value, and standard deviation. For categorical variables, absolute and relative frequencies were calculated. Descriptive statistics were used to present adverse events. Kaplan–Meier survival analysis was performed to estimate drug survival. Subgroups were compared by log-rank. Results were considered significant at p-value ≤ 0.05.

Patient demographics and characteristics at baseline are presented in Table SI[1]. The treatment characteristics are summarized in Table SII[1]. All adverse events recorded during the treatment period are summarized in Table SIII[1]. After 24 weeks of treatment, 68.2% and 40.9% of the patients treated with alitretinoin or cyclosporine, respectively, were categorized as responders. Fig. S1[1] presents the drug survival rate for cyclosporine and alitretinoin in patients with hand eczema. Median drug survival for alitretinoin and cyclosporine were 7.1 and 9.6 months, respectively. Substantial number of patients discontinued the treatment, both alitretinoin and cyclosporine, early in the treatment course. Drug survival rates showed no significant difference between the 2 groups ($p=0.168$). The drug survival may be much longer, because 11.3% and 13.8% of patients in the alitretinoin and cyclosporine groups were still active users at the time of data lock. Moreover, patients who stopped treatment due to disease control were also considered as an event, but they discontinued treatment for a positive reason.

DISCUSSION

Avoiding exposure is of primary importance to prevent hand eczema caused by allergens or irritants. This, however, is hard to practice, and most patients with chronic hand eczema require long-term treatment. The first treatment of choice is a topical steroid; however, if a patient requires long-term treatment for more than 6 weeks, close attention must be paid to the possible development of side-effects (8).

Ruzicka et al. (9) reported the efficacy and safety of oral alitretinoin in severe chronic hand eczema patients

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refractory to topical steroids. Once daily oral administration of alitretinoin (30 or 10 mg) for 24 weeks was demonstrated to yield response rates of 47.7% and 27.5%, respectively. It is recommended that 30 mg oral alitretinoin capsules to be used as a standard dose for the treatment of hand eczema.

Diepgen et al. (10) investigated the use of alitretinoin to treat chronic hand eczema in daily "real life" medical practice conditions in Germany. In total, 56.7% of patients reached a PGA rating of "almost clear" or "clear". The rate of patients responding to treatment with alitretinoin was slightly different for each subtype of hand eczema, with hyperkeratotic-rhagadi-form (59.2%), fingertip (52.2%) and vesicular (47.9%) exhibiting variable response rates.

Petersen & Menné (11) reported a case of refractory chronic vesicular hand eczema that was treated successfully with cyclosporine. The patient showed significant improvement following a daily dose of 5.0 mg/kg within 2 weeks of cyclosporine treatment. Granlund et al. (3) evaluated the efficacy of cyclosporine A and topical 0.05% betamethasone-17,21-dipropionate cream treatments in patients with chronic hand eczema after 6 weeks of treatment. There was no significant difference between the 2 groups of 41 patients, but both treatments resulted in significant disease improvement. In a retrospective drug survival study, the use of cyclosporine yielded a positive treatment response, particularly in patients with recurrent vesicular hand eczema (12).

The adverse events associated with alitretinoin were consistent with retinoid toxicity. Side-effects were usually managed by transient dose reduction or symptomatic treatment; however, headache, alopecia, elevation of liver function test, and nausea resulted in the early cessation of treatment. The adverse events associated with cyclosporine were consistent with those described in previous trials. Side-effects were usually managed with transient dose reduction or symptomatic treatment; however, hypertension, hepatotoxicity, renal toxicity, and alopecia resulted in early cessation of treatment.

One limitation of this study is the relatively small number of patients, as the study is based on a single-centre analysis. Differences in loss rates between clinical trials and daily practice are well known (13). Although randomized clinical trials are considered as the gold standard in the clinical evidence hierarchy, they cannot collect all data relevant for use in everyday clinical practice. As this study is a retrospective review of the daily use study, it is limited by a lack of blinding and lack of randomization. Moreover, selection bias may have occurred while selecting therapeutic agents.

In conclusion, this retrospective study demonstrated median drug survival of 7.1 and 9.6 months for alitretinoin and cyclosporine, respectively. After 24 weeks of treatment, responder rates in the alitretinoin- and cyclosporine-treated groups were 68.2% and 40.9%, respectively. Further evaluation is needed, comparing treatment efficacy in a head-to-head comparative study. Also, further research is needed on the effectiveness of treatment, through data collection for various subtypes of chronic hand eczema.

The authors have no conflicts of interest to declare.

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