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ORIGINAL ARTICLE

Simvastatin/Ezetimibe Therapy for Recalcitrant Alopecia Areata: An Open Prospective Study of 14 Patients

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Background: Simvastatin belongs to the statin family, whose members have immunomodulatory activities. Ezetimibe have synergetic effects when co-administered with simvastatin. In several case reports, alopecia totalis and alopecia universalis were successfully treated with simvastatin/ezetimibe, suggesting that this combination could be a new efficient therapy for recalcitrant alopecia areata (AA). **Objective:** To verify the efficacy of the simvastatin/ezetimibe combination therapy for recalcitrant AA and investigate the relationship between various treatment responses and prognostic factors. **Methods:** This prospective open study was performed in patients with recalcitrant AA with the bald surface exceeding 75%. All patients took simvastatin (40 mg) and ezetimibe (10 mg) daily. The extent of hair regrowth expressed as percentage of the bald area was used to evaluate the effectiveness of the therapy. **Results:** Of 14 enrolled patients, 4 patients (28.6%) were judged as responders showing regrowth of 30% to 80% after 3 months of treatment. The mean age of onset in non-responders was significantly lower than in responders. The total score of prognostic factors, calculated as a sum of factors related to poor prognosis, was much lower in responders than in non-responders. **Conclusion:** The remission rate in this study was unsatisfactory. However, since the recruited patients had not responded to any other treatments for AA, simvastatin/ezetimibe can still be considered as an alternative treatment for recalcitrant AA. The total scores of the prognostic factors were statistically different between responders and non-responders. These results can be used to predict the outcome of treatment with simvastatin/ezetimibe and anticipate prognosis. **(Ann Dermatol 29(6) 755~760, 2017)**

-Keywords-
Alopecia areata, Ezetimibe, Prognostic factor, Simvastatin

INTRODUCTION

Alopecia areata (AA) is a common, unpredictable, non-scarring form of hair loss without any visible signs of inflammation or skin symptoms. AA affects all age groups and different ethnicities, with an equal sex distribution[1,2]. At any given time, approximately 0.2% of the population has AA, and approximately 1.7% of the population will experience episodes of AA during their lifetime[3,4]. It is a T-cell mediated autoimmune disorder most likely to occur in genetically predisposed individuals.

There is a lack of medications of adequate efficacy for the treatment of AA. Various treatment modalities suggested to be efficient against AA are immunosuppressants, including steroids, cyclosporine, methotrexate, azathioprine, sulfasalazine, and biologics. Phototherapy (psoralen with ultraviolet A and narrow-band ultraviolet B) and topical modalities, including diphenylcyclopropenone, 1-chloro-2,4-dinitrobenzene, topical steroids, calcineurin inhibitors, mesotherapy, capsaicin, topical irritant (anthralin), and vasodilator minoxidil, are also known to be effective treatments for AA. However, the efficacy of these treatments and prognosis of AA are varied and unpredictable. These uncertainties are related to several factors that indicate poor

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prognosis in AA: extent of hair loss, an ophiasis pattern, long duration of hair loss, positive family history, presence of other autoimmune or atopic diseases, nail abnormalities, and onset at childhood or young age[5]. Moreover, in alopecia totalis (AT) and alopecia universalis (AU), the chance of full recovery is $<10\%$[6,7].

In several case reports, AT and AU were successfully treated with simvastatin/ezetimibe, indicating that this combination could be a new, effective therapy for AA[8,9]. Lattouf et al.[10] attempted to confirm the effectiveness of simvastatin/ezetimibe in a cohort of patients with AA via a pilot study.

Our study is an open prospective study, similar to the study by Lattouf et al.[10] The purpose of the present study was to verify the efficacy of the simvastatin/ezetimibe combination therapy for recalcitrant AA and investigate the relationship between various treatment responses and prognostic factors that affect the results of the therapy.

MATERIALS AND METHODS

This was a prospective open study performed on an outpatient basis during a period of 2 years, from April 2014 to March 2016. Informed consent was obtained, and the protocol was approved by the institutional review board of Kyung Hee University Hospital at Gangdong (IRB no. 2014-04-022). The inclusion criteria were as follows: (1) bald surface exceeding 75%[11], (2) no treatment received for the last 3 months, and (3) recalcitrant AA showing no response to other therapeutic modalities, including systemic steroid therapy, localized intradermal steroid injection, diphenylcyclopropenone immunotherapy, cyclosporine, inosiplex, and hydroxychloroquine. Patients with a follow-up period of <2 months or treatment duration of <3 months were excluded.

For each patient, we conducted a detailed review of clinical history, family history of AA, and personal history of associated diseases such as atopy and auto-immune disorders. Various clinical parameters were studied, including age, age of onset, duration of AA, number of recurrences, extent of alopecia, and nail involvement. The extent of hair loss was classified according to the guidelines published by Olsen et al.[11]: S1 ($<25\%$), S2 ($25\%\sim49\%$), S3 ($50\%\sim74\%$), S4 ($75\%\sim99\%$), and S5 (100%). There exist many well-known representative factors of poor prognosis: age of onset ≤13 years, family history of AA, atopy, AT/AU, ophiasis pattern, duration of AA ≥1 year, nail involvement, and autoimmune disease[12,13]. We calculated the total sum of these factors, with each factor contributing 1 point (range of the total score: 0 to 8).

A complete physical examination and the following laboratory tests were performed: complete blood cell count; thrombocyte count; erythrocyte sedimentation rate; levels of glucose, nitrogen, potassium, chloride, carbon dioxide, proteins, urea, creatinine, calcium, alkaline phosphatase, bilirubin, alanine aminotransferase, aspartate aminotransferase, *g*-glutamyltransferase, thyroxine, and thyroid-stimulating hormone; rapid plasma regain; urinalysis; and autoantibody (antinuclear antibody) screening.

Treatment modality

Simvastatin (40 mg) and ezetimibe (10 mg) were administered daily for 3 months with oral medication. At baseline and after 3 months of treatment, global photography and standard laboratory tests were performed. The patients were also evaluated for adverse effects.

Hair growth was assessed on a percentage scale ranging from 0% to 100% of the total scalp surface. The patients were examined at 1, 3, and 6 months after 3 months of treatment. At each visit, response rate and adverse effects were evaluated. The main outcome was the percentage of pretreatment bald area covered by hair regrowth at 1, 3, and 6 months. A responder was defined as a subject with hair regrowth of $>20\%$ compared with the initial state after 3 months of treatment. A relapse was defined as hair loss of $>25\%$ during the follow-up.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 23.0 software (IBM Co., Armonk, NY, USA). Differences in ordinal and continuous variables were assessed with the Mann-Whitney U test. A two-tailed *p*-value of <0.05 was considered to indicate a statistically significant difference.

RESULTS

Demographic patterns and clinical aspects

Fourteen patients with AA unresponsive to other therapeutic modalities were included in this study. The age of the patients with AA ranged from 18 to 51 years (mean$\pm$standard deviation, 32.5 ± 10.46 years). The age of onset ranged from 10 to 42 years (21.57 ± 9.64 years). Five patients (35.7%) were male and 9 (64.3%) were female. The male-to-female ratio was 1:1.8. Four patients (28.6%) experienced the first episode of AA before the age of 13 years and had a positive family history of AA. The disease duration ranged from 0.5 to 27 years (10.96 ± 8.39). Five patients (35.7%) had a history of atopy (namely, atopic dermatitis, asthma, and allergic rhinitis), and nail changes were found in 3 patients (21.4%). Three patients (21.4%) had at least one autoimmune disease

Table 1. Demographic patterns and results after 3 months of treatment in 14 patients with recalcitrant AA

Patient no.	Age (yr)	Sex	Regrowth after 1 mo (%)	Regrowth after 3 mo (%)	Relapse and follow-up 6 mo (%)	Family history of AA	Atopy	Clinical variants	Ophiasis pattern at the start	Disease duration (yr)	Nail involvement	Autoimmune disease	Total prognostic factor score
Responders to simvastatin/ezetimibe													
2	42	M	20	80	80	−	−	AT	−	0.5	−	−	1
7	25	F	10	30	30	−	−	AU	+	5	−	−	3
10	32	F	50	70	70	−	−	AT	−	3	−	−	2
13	41	M	None	40	Relapse after 6 months	−	−	AU	−	10	−	−	2
Nonresponders to simvastatin/ezetimibe													
1	23	F	None	-	-	+	+	AA	−	5	+	−	5
3	18	F	None	-	-	−	+	AU	−	6	−	−	4
4	39	M	None	-	-	−	+	AU	+	21	+	Vitiligo	6
5	19	F	None	-	-	+	−	AT	+	6	−	−	5
6	23	F	None	-	-	−	−	AT	−	1	−	−	1
8	31	M	None	-	-	−	−	AA	−	16	−	−	2
9	46	F	None	-	-	−	−	AU	+	17	−	Hyperthyroidism	4
11	38	M	None	-	-	+	+	AT	−	27	+	−	6
12	51	F	None	-	-	+	−	AT	−	19	−	Hyperthyroidism	4
14	27	F	None	-	-	−	+	AT	−	17	−	−	4

AA: alopecia areata, M: male, F: female, AT: alopecia totalis, AU: alopecia universalis, -: no growth.

such as thyroid dysfunction or vitiligo. At the time of presentation, 12 patients (85.7%) had AT or AU (S5) and 2 patients (14.3%) had patchy alopecia with a scalp involvement of >75% (S4). Four patients (28.6%) experienced an ophiasis pattern involvement of AA at the first episode. Data are shown in Table 1.

Responses to simvastatin/ezetimibe therapy according to prognostic factors

Of the 14 enrolled patients, 4 (28.6%) were considered responders. Hair regrowth was evident after 1 month of treatment in 3 patients and after 3 months in 1 patient, who had a relapse after 6 months of follow-up. All the responders showed 30% to 80% regrowth at 3 months, and this regrowth rate persisted at 6 months in 3 patients (Fig. 1). The mean disease duration in responders and non-responders was 4.6 years (4.63±4.03) and 13.5 years (13.50±8.44), respectively. The mean disease duration was substantially lower in responders, but the difference was not statistically significant (p=0.061, Fig. 2A). The age of onset in responders and non-responders ranged from 20 to 42 years (30.50±9.04) and from 10 to 32 years (18.00±7.57), respectively. The mean age of onset in non-responders was significantly lower than in responders (p=0.039, Fig. 2B).

We calculated the total sum of factors related to poor prognosis of AA for each patient. This total score varied from 1 to 6. The scores of the responders and non-responders ranged from 1 to 3 (2.0±0.82) and from 1 to 6 (4.1±1.60), respectively. The total score of the prognostic factors was significantly lower in responders (p=0.045, Fig. 3). The corresponding data are shown in Table 1.

Adverse effects

The patients were also evaluated for adverse effects. There were no adverse effects such as mild headache or muscle cramps during the treatment period.

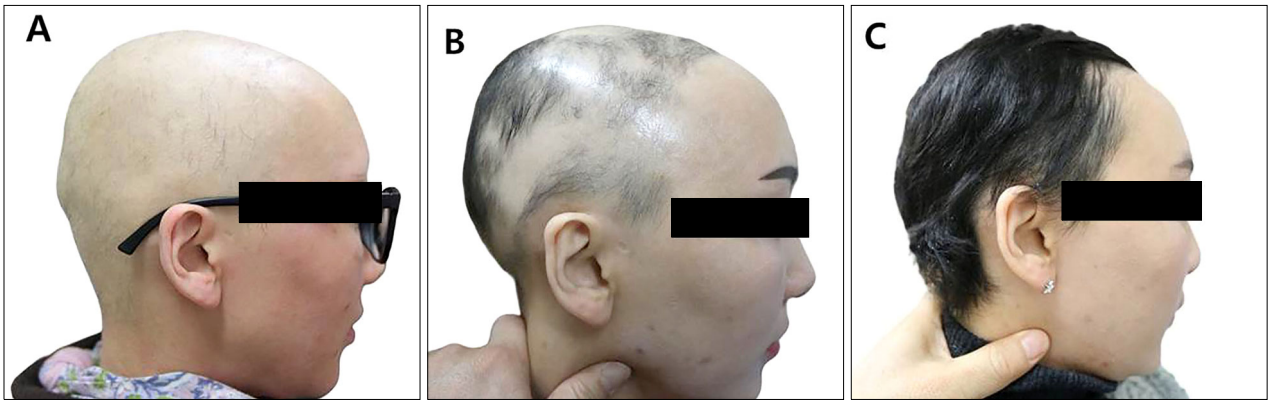

Fig. 1. Alopecia areata. Patient no. 10 is a responder with preservation of the regrown hair. (A) Before treatment, (B) 3 months after treatment, (C) 6 months after treatment.

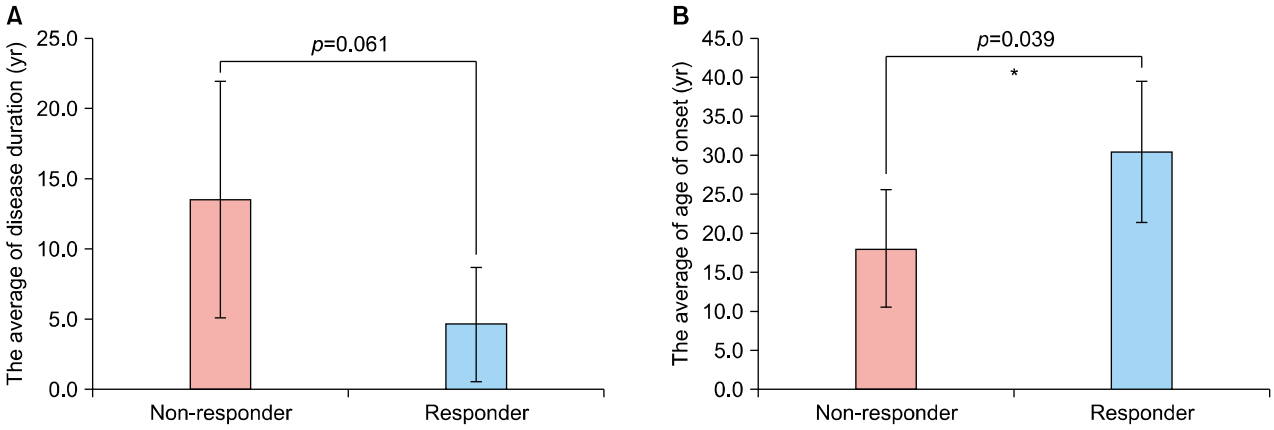

Fig. 2. The differences in mean disease duration (A) and mean age of onset (B). The Mann-Whitney U test was used to compare the groups. *Stastically significant, p<0.05.

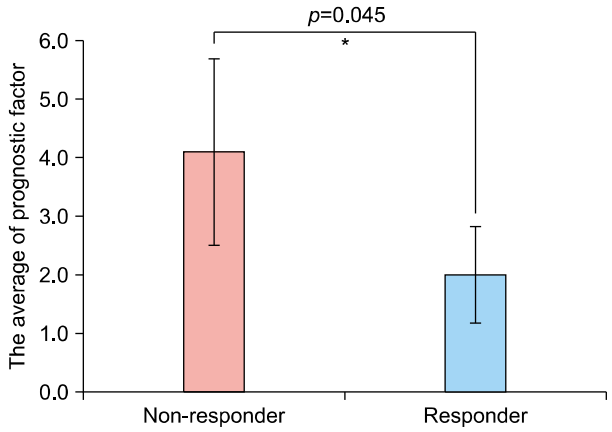

Fig. 3. The average total scores of prognostic factors. The Mann-Whitney U test was used to compare the groups. *Stastically significant, $p<0.05$.

DISCUSSION

Simvastatin belongs to the statin family, whose members are 3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitors. Statins are used in clinical practice to lower lipid levels[14]. In addition, statins have immunomodulatory activities, which contribute to the inhibition of the expression of major histocompatibility complex (MHC) class II[15]. The characteristic histopathological findings in intrafollicular and perifollicular lymphocytic infiltrates, with a predominance of $CD4^+$ T-cells, are accompanied by the expression of intercellular adhesion molecule 1 (ICAM-1) on the epithelium of the follicle[14]. Statins act not only to directly inhibit MHC-II expression but also to block lymphocyte function-associated antigen 1, resulting in decreased adhesion of lymphocytes to ICAM-1 in hair follicles[13]. Repression of MHC class II and reduction of lymphocyte binding to ICAM-1 may play major roles in hair regrowth in patients with AA.

Ezetimibe is the first member of a new class of lipid-lowering compounds that reduce cholesterol levels by inhibiting its absorption in the intestine. Ezetimibe may be responsible for the immunomodulatory and synergetic anti-inflammatory effects when co-administered with simvastatin. Even though ezetimibe by itself does not affect C-reactive protein levels, a significant reduction in the C-reactive protein level was observed when ezetimibe was combined with simvastatin[8]. When only ezetimibe was administered to patients with AA, no significant improvement in hair regrowth was observed. However, hair began to grow shortly after simvastatin was added[16].

Lattouf et al.[10] performed a small prospective cohort study aimed at evaluating the efficacy of the simvastatin and ezetimibe combination therapy for AA. Of the 19 patients who completed 24 weeks of treatment with simvastatin/ezetimibe, 14 were judged as responders, and 74% maintained the regrown hair or showed further regrowth at follow-up. In our study, 4 (28.6%) of the 14 patients showed partial responses to the combination therapy. The remission rate was unsatisfactory. The poor rate of therapeutic response precludes the routine use of the simvastatin/ezetimibe therapy. The simvastatin/ezetimibe therapy for AA was also ineffective in the recent report of Loi et al.[17]. However, clinicians should not conclude that this combination therapy is not effective for AA, as the patients in the present study did not respond to any other treatments of AA. Simvastatin/ezetimibe can be considered as an alternative treatment for recalcitrant AA.

We attempted to quantitate the prognostic factors of each patient with AA by calculating the total prognostic factor score. We found a statistically significant difference in the mean score between the responders and non-responders (2.0 ± 0.82 and 4.1 ± 1.60, respectively; $p<0.05$). Moreover, the difference in age of onset between the responders and non-responders was the most prominent clinical factor; therefore, it can be expected that age of onset has the strongest effect on prognosis. Although the difference in disease duration was remarkable, it did not reach the level of statistical significance, likely because of the small sample size and large SD. These results can be used to predict the outcome of treatment of recalcitrant AA with simvastatin/ezetimibe and anticipate prognosis. The mean durations of the current AA episode before starting treatment in responders and non-responders (2.4 vs. 11.1 years, respectively) were similar to the values obtained by Lattouf et al.[10].

The limitations of this study are the small number of patients, relatively short follow-up period, and variations in treatment regimens before the start of the simvastatin/ezetimibe combination therapy. Nevertheless, our results indicate that the combination of simvastatin and ezetimibe can be an alternative treatment modality for patients with recalcitrant AA with lower prognostic factor scores. These findings warrant future randomized placebo-controlled clinical trials in larger cohorts with precisely defined demographic features of patients.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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