学 位 論 文 の 要 旨

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学　位　論　文　名	Interleukin-8 Levels in the Stratum Corneum as a Biomarker for Monitoring Therapeutic Effect in Atopic Dermatitis Patients
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論 文 内 容 の 要 旨

INTRODUCTION

The stratum corneum contains several growth factors and cytokines that are synthesized in keratinocytes. The tape-stripping technique has been studied as a noninvasive and relatively quick and simple method for estimating cytokine concentrations in the stratum corneum. We previously reported that the amount of interleukin-8 in the stratum corneum (scIL-8) is related to the severity of local skin inflammation in atopic dermatitis (AD). However, it is unknown whether scIL-8 levels reflect pharmacologic responses to a therapeutic intervention in AD patients. The preferred first-line therapy recommended for AD treatment is topical corticosteroid treatment. Therefore, in this study, we aimed to investigate whether the improvement of dermatitis in AD is correlated with scIL-8 levels before and after topical corticosteroid treatment.

MATERIALS AND MRTHODS

We enrolled 22 patients (11 males and 11 females) from Shimane University Hospital who met the diagnostic criteria for AD established by the Japanese Dermatological Association. Topical corticosteroid treatment was administered for 4–6 weeks. Three sites were chosen for the evaluations—the inside of the forearm, abdomen, and area with the most severe symptoms in each patient. Visual skin score evaluation, scIL-8 measurement, transepidermal water loss (TEWL) and skin water content measurement were performed at day 0 (first visit), 2 weeks later (second visit), and 4–6 weeks later (third visit), and blood examination was performed at the first and third visits. Skin scores were assessed visually for each of the three skin sites to assess the severity of the disease using seven SCORAD index parameters (erythema, edema, lichenification,

oozing/exudation, excoriation, xerosis/dryness, and itch). According to increasing symptom severity, each parameter was scored from 0 to 3, for a total possible score of 21. Stratum corneum samples were collected by using the noninvasive tape-stripping method. The stratum corneum obtained by the tape-stripping method were used to measure IL-8 level using IL-8-specific ELISA kit after extraction with extraction buffer. scIL-8 concentration was expressed as pg per mg of protein content of the stratum corneum. TEWL and skin water content were measured at each skin site by Tewameter and Corneometer, respectively. Blood was collected to assess the white blood cell count, %eosinophil, serum levels of lactate dehydrogenase (LDH), total IgE, and thymus and activation-regulated chemokine (TARC).

The study protocol was approved by the Research Ethics Committee of Shimane University (Approval No. 1473).

RESULTS AND DISCUSSION

The average scIL-8 in the patients before the treatment was 790 ± 348 pg/mg on the forearm, 902 ± 391 pg/mg on the abdomen, and 1905 ± 500 pg/mg over the lesions with the most severe symptoms at the first visit. Significant correlations were observed between scIL-8 and skin scores on the forearm ($rs = 0.50$, $P<0.001$), on the abdomen ($rs = 0.37$, $P <0.01$), and on the area with the most severe symptoms ($rs = 0.53$, $P<0.001$).

With topical corticosteroid treatment, scIL-8 levels on the forearm reduced significantly from 790 ± 348 pg/mg at the first visit to 163 ± 68 pg/mg at the second visit and 100 ± 37 pg/mg at the third visit. Additionally, scIL-8 levels on the abdomen reduced significantly from 902 ± 391 pg/mg at the first visit to 165 ± 57 pg/mg at the second visit and 142 ± 38 pg/mg at the third visit. On the skin lesion with the most severe symptoms, a higher reduction of scIL-8 level was found, from 1905 ± 500 pg/mg at the first visit to 267 ± 108 pg/mg at the second visit and 243 ± 65 pg/mg at the third visit.

The average skin scores before the treatment were 7.8 ± 1.0 on the forearm, 7.3 ± 0.9 on the abdomen, and 10.4 ± 0.9 over the skin lesion with the most severe symptoms. The average skin score on the forearm reduced significantly to 4.0 ± 0.7 at the second visit and 2.0 ± 0.4 at the third visit. On the abdomen, it reduced to 1.9 ± 0.4 at the second visit and 1.5 ± 0.3 at the third visit. On skin lesion with the most severe symptoms, the average skin score reduced significantly to 3.5 ± 0.6 at the second visit and 2.5 ± 0.5 at the third visit.

ΔscIL-8 (difference between the values at first and third visits) was significantly correlated with the Δskin score (difference between the values at first and third visits) in the forearm ($rs = 0.50$, $P<0.01$), abdomen ($rs = 0.82$, $P<0.001$), and area with the most severe symptoms ($rs = 0.55$, $P<0.01$). Similar significant correlations were observed between the ΔscIL-8 (difference between the values at first and second visits) and the Δskin score (difference between the values at first

and second visits) for all three sites, and between the ΔscIL-8 (difference in the values at second and third visits) and Δskin score (difference in the values at second and third visits) for the abdomen and area with the most severe symptoms. Thus, the reduction in scIL-8 levels was associated with the improvement in local skin severity in AD.

Additionally, the average TEWL values decreased significantly at the second and third visits compared to those at the first visit at all three sites. Skin water content increased significantly at the third visit compared to those at the first visit at all three sites. When the ΔscIL-8 and ΔTEWL were analyzed between the first and third visit, there were no significant correlation in the forearm (rs = 0.16), abdomen (rs = 0.33), or in the areas with the most severe symptoms (rs =0.20). However, when ΔscIL-8 and Δskin water content were analyzed between the first and third visits, a significant correlation was observed in the abdomen (rs = 0.41, $p<0.05$). We also found that scIL-8 levels, along with blood biomarker levels, serum TARC, serum LDH, and %eosinophil, decreased significantly after the treatment.

The limitations of this study are its relatively small sample size (n=22) and the absence of potent pharmaceutical treatments other than topical corticosteroid treatment.

CONCLUSION

The scIL-8 concentration decreases with improvements in skin symptoms in AD patients after topical corticosteroid treatment; thus, it may be a suitable biomarker for monitoring therapeutic effects on the lesion severity of AD patients.