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FTY720 Regulates Bone Marrow Egress of Eosinophils and Modulates Late-Phase Skin Reaction in Mice

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Eosinophilia in the blood and skin is frequently observed in patients with certain inflammatory skin diseases, such as atopic dermatitis. However, the mechanism underlying eosinophil circulation and the role of eosinophils in cutaneous immune responses remain unclear. In repeated hapten application-induced cutaneous responses in BALB/c mice, the administration of FTY720 before the last challenge decreased the number of skin-infiltrating eosinophils and reduced the late-phase reaction. A similar reduction of the late-phase reaction was observed by a sphingosine-1-phosphate G protein-coupled receptor (S1P1)-selective agonist, SEW2871. We monitored numerous alterations of eosinophils in the blood, spleen, bone marrow, and lymph nodes of interleukin-5 transgenic mice, used as an eosinophilia model, following FTY720 administration. The number of circulating eosinophils was significantly decreased after treatment with FTY720, and eosinophils accumulated in the bone marrow. In addition, eosinophils expressed S1P1, S1P3, and S1P4 mRNAs, and their chemotactic response to S1P was abolished by FTY720 as well as by SEW2871. These findings suggest that FTY720 affects the number of eosinophils in both the blood and skin by inhibiting the egress of eosinophils from the bone marrow and thus downmodulating the late-phase reaction. (*Am J Pathol* 2010, 177:1881–1887; DOI: 10.2353/ajpath.2010.100119)

Eosinophils are thought to be involved in the pathogenesis of several skin disorders. For example, atopic dermatitis is characterized by an infiltrate of inflammatory

cells, mainly consisting of CD4⁺ memory T cells, but distinct eosinophils constitute the inflammatory infiltrate in conjunction with T cells.¹ The trafficking of eosinophils into inflammatory sites is regulated by a number of cytokines such as Th2 cell-derived interleukin (IL)-4, IL-5, and IL-13, chemokines such as regulated on activation normal T cell expressed and secreted/CCL5, and the eotaxins/CCL11 and adhesion molecules.^{2–6}

Although accumulating studies have provided a significant insight on the association of cytokines and chemokines with cutaneous tissue eosinophilia, little information exists on eosinophil localization and functional role of cutaneous eosinophils.⁷ To study eosinophil kinetics and recruitment, IL-5 transgenic mice have been established and used as an eosinophilia model.⁸ In our preliminary study, when IL-5 transgenic mice were repeatedly sensitized to hapten and subsequently challenged with the same antigen, mice developed a late-phase cutaneous reaction and tissue eosinophilia, suggesting that eosinophils may be involved in the establishment of cutaneous late-phase reactions. Therefore, we speculated that the migration of eosinophils from lymphoid organs is a crucial step in the eosinophil localization to the skin, and this migration could be targeted to prevent the development of cutaneous diseases.

Sphingosine-1-phosphate (S1P) is a biologically active metabolite of plasma-membrane sphingolipids that is essential for immune-cell trafficking.⁹ The immune functions of S1P result from the engagement of five subtypes of G protein-coupled receptors, S1P1–S1P5. Initial studies for evaluating the roles of S1P were performed with the compound FTY720. S1P1 expression on T cells determines the retention of naïve T cells, but not memory T cells, in

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lymph nodes and their exit into the lymph in response to the S1P gradient,^{10,11} thereby modulating immune responses *in vivo*.¹² Moreover, recent studies have identified that S1P is required for natural killer cell egress from lymph nodes and bone marrow.¹³ These findings raise a possibility that S1P and S1P receptors may function in the egress of lymphoid organs of eosinophils. However, the mechanism of migration of eosinophils from the lymphoid organs into the peripheries remains unelucidated.

In this study, we investigated the modulatory effect of FTY720 on eosinophil and late-phase reaction in mice. We evaluated the migration and trafficking of eosinophils between the systemic circulation and the skin. FTY720 inhibited eosinophil infiltration into the skin and attenuated the late-phase reaction of the skin. Our results propose a novel therapeutic approach of FTY720 on eosinophil localization and trafficking.

Materials and Methods

Animals and Reagents

Female C57BL/6 (B6), BALB/c, and New Zealand White (NZW) mice were purchased from Japan SLC (Hamamatsu, Japan). All experiments were conducted on 8-week-old mice. IL-5 transgenic mice were obtained from RIKEN BioResource Center (Tsukuba, Japan). These mice were maintained on a 12-hour light/dark cycle under specific pathogen-free conditions. All protocols were approved by the Institutional Animal Care and Use Committee of the University of Occupational and Environmental Health. 2,4,6-Trinitrochlorobenzene (TNCB) was obtained from Tokyo Kasei (Tokyo, Japan).

For treatment with FTY720 (Cayman Chemical, Ann Arbor, MI), mice were injected i.p. with 3.0 mg/kg FTY720 or with an equivalent volume of normal saline as a control at the indicated time points. Alternatively, mice were administered with S1P1 selective agonist SEW2871 (Calbiochem, San Diego, CA) before the final TNCB challenge by gavage because of its low solubility in aqueous solution. SEW2871 was dissolved in 10% dimethyl sulfoxide and diluted with 25% Tween 20 as described previously.¹⁴ The dosage of 20 mg/kg was chosen based on the previous study showing a consistent lymphocytopenia up to 12 hours.¹⁴

Flow Cytometry

For flow cytometry, cells were plated at a density of 1×10^6 cells/well in 96-well U-bottomed plates (Falcon; BD Biosciences, San Jose, CA). Cells were stained for 20 minutes on ice with monoclonal antibodies (mAbs) in 25 μ l of PBS containing 2% FCS, 1 mmol/L EDTA, and 0.1% Na₃ and washed twice with 200 μ l of this buffer. Data were collected on a FACSCanto system (BD Biosciences) and analyzed with FlowJo software (Tree Star, San Carlos, CA). The mAbs used were as follows: fluorescein isothiocyanate-conjugated anti-CD4 mAb, phosphatidylethanolamine-conjugated anti-Siglec-F mAb, phosphatidylethanolamine-Cy5-conjugated anti-CD8 mAb, antigen-presenting cell-conjugated anti-B220 mAb (all from BD Biosciences),

and phosphatidylethanolamine-Cy7-conjugated anti-Gr-1 mAb (eBioscience, San Diego, CA). Eosinophils were detected as Siglec-F⁺Gr-1^{int+} population.^{15,16} The number of cells was determined by flow cytometry using Flow-Count Fluorospheres (Beckman Coulter, Fullerton, CA).¹⁷

Inflammatory Skin Disease Model and Histology

BALB/c mice were sensitized through the application of 50 μ l of 3% TNCB in 4:1 acetone/olive oil to their shaved abdomens on day 0. They were challenged on both sides of each ear with 20 μ l of 0.2% TNCB in 1:9 acetone/olive oil on day 5 to evaluate contact hypersensitivity. To evaluate the inflammatory skin disease, mice sensitized in the same way 5 days before the first elicitation (day 0) were repeatedly challenged on the originally elicited ears with 20 μ l of 0.2% TNCB in 1:9 acetone/olive oil from days 8 to 29 at 3-day intervals as outlined in a previous report, with some modifications.¹⁸ On day 30, they were then challenged on both sides of each ear with 20 μ l of 0.2% TNCB in 1:9 acetone/olive oil. Ear thickness change was calculated as follows: (ear thickness after final challenge) – (ear thickness before final challenge). FTY720 was applied by i.p. injection (3 mg/kg body weight) 24 hours before final TNCB challenge.

At 48 hours after the challenge with hapten, the ears of the mice were excised for histology and fixed in 10% formaldehyde. Five-micrometer-thick sections were prepared and stained with H&E. Papanicolaou staining was used for eosinophil evaluation.

5- (and 6-)Carboxyfluorescein Diacetate Succinimidyl Ester Cell Labeling and Tracking

The axillary and inguinal lymph node cells, splenocytes, blood cells, and bone marrow cells from IL-5 transgenic mice were prepared, and single-cell suspensions were labeled with 6.5 μ mol/L 5- (and 6-)carboxyfluorescein diacetate succinimidyl ester (CFSE) (Molecular Probes, Eugene, OR) as outlined in a previous report.⁶ Twenty-four hours before cell transfer, wild-type NZW mice were injected i.p. with 3 mg/kg FTY720 or normal saline. The cells resuspended in RPMI 1640 containing 0.2% FCS were injected i.v. in NZW mice (2×10^7 cells/mouse). Twelve hours after the cell transfer, the number of fluorescent cells in the bone marrow was enumerated by flow cytometry.

Effect of IL-5 and FTY720 on Levels of Circulating and Bone Marrow Eosinophils

B6 mice were administered with or without FTY720, and 24 hours later, the mice were injected i.v. with 100 μ l of PBS containing IL-5 (500 pmol/kg) or PBS alone according to methods outlined in a previous study, with some modifications.¹⁹ Blood and bilateral femurs were taken 1 hour after i.v. injection of IL-5, and the number of eosinophils was determined by flow cytometry.

Cell Sorting and Quantitative PCR

Eosinophils and CD4⁺ T cells from the bone marrow of IL-5 transgenic mice were isolated with a cell sorter (FACSaria II; BD, Franklin Lakes, NJ). The purity of the sorted cells was typically >95%. RNA was prepared from sorted cells with RNeasy (Qiagen, Valencia, CA), and cDNA was used for quantitative PCR. Murine S1P receptor expressions were quantified using TaqMan Gene Expression Assay (Applied Biosystems, Foster City, CA) in the ABI PRISM 7000 sequence detection system (Applied Biosystems) as follows: S1P1 (Assay ID: Mm00514644_m1), S1P2 (Assay ID: Mm01177794_m1), S1P3 (Assay ID: Mm00515669_m1), S1P4 (Assay ID: Mm00468695_s1), and S1P5 (Assay ID: Mm00474763_m1). As an endogenous reference for these PCR quantification studies, β -actin gene expression was measured using the TaqMan rodent β -actin control reagents (Applied Biosystems). The relative expression was calculated using the $2^{-\Delta\Delta C_T}$ method.²⁰ The expression of the target gene normalized to an endogenous, β -actin, reference and relative to a calibrator was given by the formula $2^{-\Delta\Delta C_T}$. Gene expression in untreated mice was used as the calibrator to calculate $\Delta\Delta C_T$.

Chemotaxis Assay

Eosinophils in the bone marrow of IL-5 transgenic mice were tested for transmigration across uncoated 5- μ m Transwell filters (Corning Costar, Corning, NY) to S1P (Sigma-Aldrich, St Louis, MO) or medium in the lower chamber over 3 hours. In some experiments, the cells were pretreated with FTY720 or SEW2871 described previously.²¹ The migrated cells were enumerated by flow cytometry.²² The medium used in this assay was RPMI

1640 with 0.5% fatty acid-free bovine serum albumin (Calbiochem, San Diego, CA).

Statistical Analysis

Data were analyzed using an unpaired two-tailed *t*-test. $P < 0.05$ was considered to be significant.

Results

Reduction of Eosinophil Infiltration into the Skin by FTY720 in a Murine Repeatedly Hapten-Challenged Dermatitis

In a murine model of contact hypersensitivity, repeated application of a hapten such as TNCB to the same skin site in BALB/c mice results in a shift from a typical delayed-type hypersensitivity to an immediate type one. As a result, the late-phase reaction and eosinophil infiltration occur, usually 4 to 8 hours after the final challenge.¹⁸ We used this model to evaluate the effect of FTY720 on tissue eosinophilia. Skin infiltration of eosinophils was inhibited by FTY720 treatment, but infiltration of lymphocytes was not changed (Figure 1A). This was further confirmed by Papanicolaou staining, which showed reduced eosinophil infiltration by FTY720 (Figure 1B).

Impairment of Cutaneous Late-Phase Reaction by FTY720 in IL-5 Transgenic Mice

A previous study has demonstrated that the late-phase reaction caused by repeated painting with hapten is po-

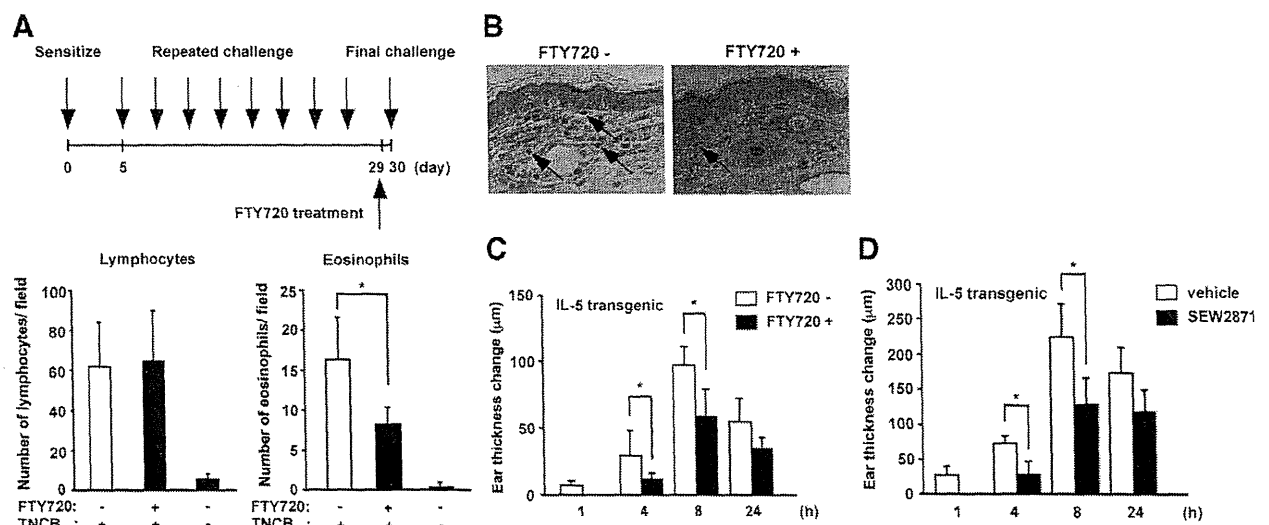


Figure 1. Effect of FTY720 on eosinophil accumulation in the skin. **A:** BALB/c mice were sensitized with TNCB on their shaved abdomens on day 0. They were then challenged on both sides of each ear on day five. The mice were repeatedly challenged on the original sensitized ears with 0.2% TNCB from days 8 to 29 at 3-day intervals. At 48 hours after the final challenge, histological sections were prepared from the skin. The total numbers of lymphocytes and eosinophils were counted in five high-power fields. * $P < 0.05$. **B:** Representative pictures of skin sections from control and FTY720-treated mice challenged with TNCB. Data are from two independent experiments. Arrows indicate eosinophils. **C:** The ear swelling responses were measured before and at 1, 4, 8, and 24 hours after the final challenge. Data are from three independent experiments. * $P < 0.05$. **D:** Similar results were obtained when mice were treated with SEW2871. Data are from two independent experiments. * $P < 0.05$.

tentiated in IL-5 transgenic mice.⁸ This enhancement may be related to tissue eosinophilia in the skin. Therefore, we investigated the significance of FTY720 on cutaneous late-phase reaction *in vivo* using IL-5 transgenic mice. IL-5 transgenic mice were sensitized with TNCB on day 0 and elicited with TNCB on the abdomen from days 5–29 at 3-day intervals. On day 30, they were challenged on both sides of each ear.

The treatment of mice with FTY720 12 hours before the challenge yielded reduced ear swelling responses at 4 and 8 hours after challenge (Figure 1C). Because the skin infiltration of eosinophils was suppressed by FTY720, the data were interpreted to result from the direct effect of FTY720 on eosinophils. Similar findings were observed when SEW2871 were administered (Figure 1D).

Numerical Alterations of Eosinophils after FTY720 Treatment

To clarify the mechanisms underlying the FTY720-induced reduction of skin eosinophils, we first evaluated the kinetics of eosinophils in the blood. It is known that FTY720 inhibits T cell egress from the secondary lymph nodes and decreases circulating T cells.^{23–26} We examined the time course of decrease in the circulating Siglec-F⁺Gr-1^{int} eosinophils after treatment of IL-5 transgenic mice with FTY720. The blood was drawn by intraocular venipuncture before and 1, 3, 5, and 7 days after FTY720 administration. The number of eosinophils was decreased markedly 1 to 5 days after FTY720 treatment and returned to the baseline level on day 7 (Figure 2). A similar reduction of circulating eosinophils was observed 6 hours after SEW2871 administration: vehicle, $13.6 \pm 2.0 \times 10/mm^3$; and SEW2871 treatment, $2.2 \pm 0.1 \times 10/mm^3$ ($P < 0.001$, mean $\pm$ SD of three mice). However, the decreased number of eosinophils in the blood returned to the normal range 48 hours after treatment with SEW2871 ($12.5 \pm 2.1 \times 10/mm^3$).

Because blood eosinophils were decreased by FTY720, we examined the localization of eosinophils after treatment with FTY720. At 24 hours after administration of

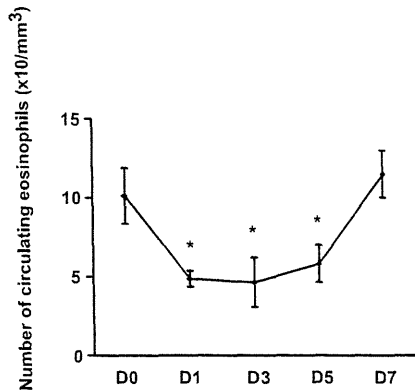


Figure 2. Numerical alterations of eosinophils in the peripheral blood following FTY720 administration. FTY720 was administered to IL-5 transgenic mice, and peripheral blood samples were periodically collected. Data are expressed as the mean $\pm$ SD. Data are from three independent experiments. * $P < 0.05$.

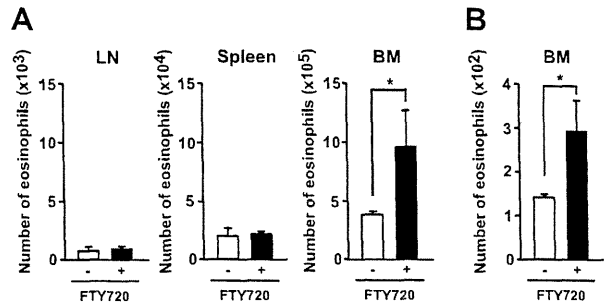


Figure 3. Accelerated accumulation of eosinophils by FTY720 in the bone marrow. **A:** FTY720 was administered to IL-5 transgenic mice. At 24 hours, lymph node cells, splenocytes, and bone marrow cells were harvested, and single-cell suspensions were analyzed by FACS for the presence of eosinophils. The homing of eosinophils to the bone marrow in the IL-5 transgenic mice was higher than that in the control mice. **B:** CFSE-labeled cells from IL-5 transgenic mice were adoptively transferred into control or FTY720-treated wild-type NZW mice. After 12 hours, the mice were killed, and eosinophils were harvested. Single-cell suspensions were analyzed by flow cytometry for the presence of CFSE-positive donor eosinophils. Error bars indicate the mean $\pm$ SEM from at least four mice per group. Data are from three independent experiments. * $P < 0.05$.

FTY720, the levels of eosinophils homing to the lymph nodes and spleen remained unchanged, but the number of eosinophils in the bone marrow increased (Figure 3A).

To examine the involvement of S1P in the regulation of eosinophil trafficking, CFSE-labeled cells collected from IL-5 transgenic mice were adoptively transferred to wild-type naïve NZW mice treated with or without FTY720. Treatment of the mice with FTY720 increased the number of CFSE-labeled eosinophils in the bone marrow (Figure 3B). These results suggest that FTY720 regulates the localization of eosinophils by inhibiting the egress of eosinophils from the bone marrow.

Inhibition of IL-5-Induced Eosinophilia by FTY720 Treatment

It is known that i.v. administration of IL-5 induces a rapid and sustained increase in the number of circulating eosinophils by mobilization from the bone marrow in B6 mice.¹⁹ In confirmation of this notion, i.v. administration of 500 pmol/kg IL-5 induced pronounced blood eosinophilia in B6 mice (Figure 4, A and B). This increase was attenuated by treatment with FTY720 (Figure 4, A and B). In another study, B6 mice were pretreated with or without FTY720, and IL-5 was injected i.v. 24 hours later. The number of eosinophils was significantly increased in the bone marrow of FTY720-treated mice 12 hours after injection (Figure 4C). Thus, FTY720 depresses the recruitment of eosinophils from the bone marrow pool to the blood.

S1P Receptor mRNA Expressions in Eosinophils

To measure S1P receptor abundance in eosinophils, bone marrow cells were prepared from IL-5 transgenic mice, and Siglec-F⁺Gr-1^{int} eosinophils and CD4⁺ T cells were purified by a cell sorter. We evaluated the expression levels of S1P receptor mRNAs by quantitative PCR. S1P1, S1P3, and S1P4 mRNAs were expressed in eosin-

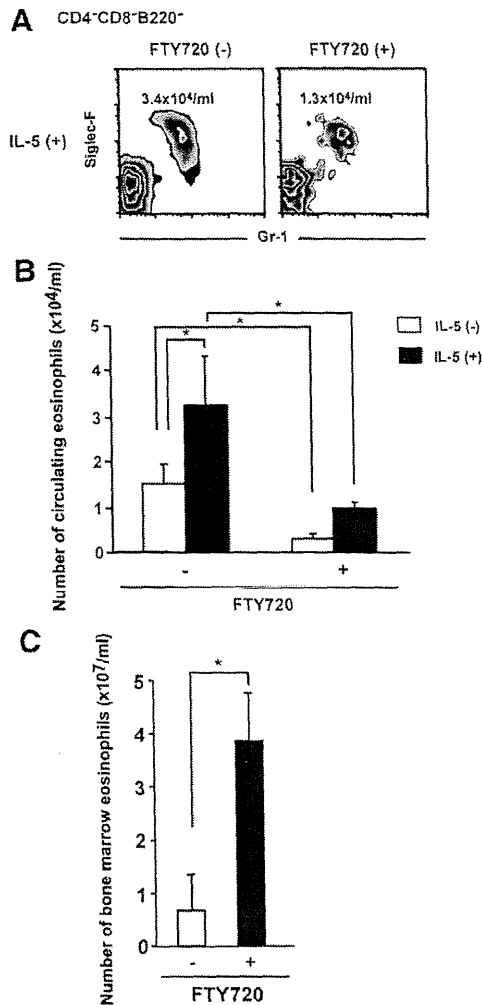


Figure 4. Effect of FTY720 after i.v. administration of IL-5 on circulating and bone marrow eosinophils. **A–C:** FTY720 was i.p. injected into B6 mice 24 hours before IL-5 injection. Mice were injected with IL-5 or vehicle alone. **A** and **B:** Circulating eosinophil numbers were determined 1 hour after injection of IL-5. **C:** After 12 hours, bone marrow samples were harvested, and single cell suspensions were analyzed by flow cytometry for the presence of eosinophils. Error bars indicate the mean $\pm$ SEM from at least four mice per group. Data are from three independent experiments. **P* < 0.05.

ophils, and their levels were higher than those in keratinocyte cell line PAM212. In contrast, S1P1 mRNA level was higher in T cells than eosinophils, and S1P4 level was comparable in T cells and eosinophils (Figure 5).

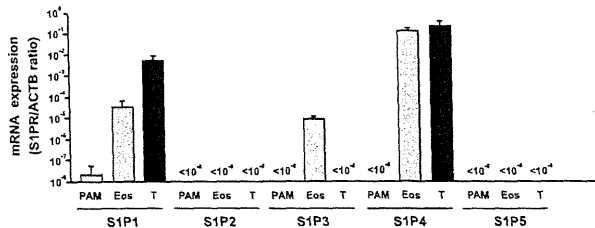


Figure 5. Quantitative PCR analysis of S1P receptor mRNAs from eosinophils. Bone marrow cells from IL-5 transgenic mice were sorted into Siglec-F⁺Gr-1^{int} eosinophils and CD4⁺ T cells. The amounts of S1P receptor mRNA were expressed as relative amounts of S1P receptor mRNA normalized to β -actin. Data are from two independent experiments.

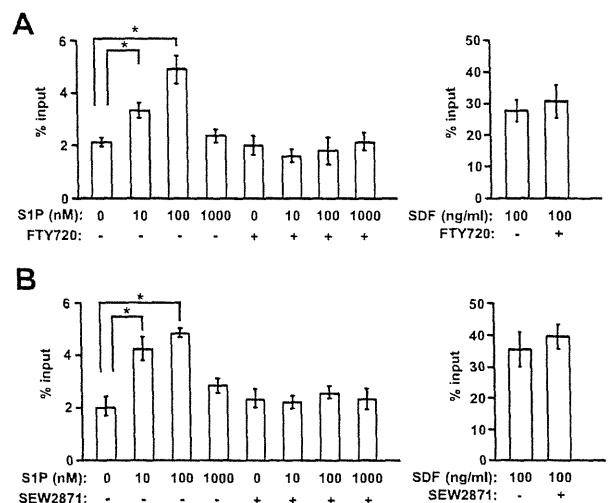


Figure 6. Chemotactic response of eosinophils to S1P. **A:** Bone marrow cells were prepared from IL-5 transgenic mice with or without FTY720. **B:** In some experiments, bone marrow cells were pretreated with 1000 nmol/L SEW2871. Chemotactic activities of eosinophils to stromal cell-derived factor 1 (SDF) were unaffected by treatment with either FTY720 or SEW2871. **A** and **B:** Input cells and cells that migrated to the lower well of the Transwell chamber in the absence of chemokine or in response to S1P were analyzed by flow cytometry to detect eosinophils. Bars represent means of triplicated Transwells, and data are from three independent experiments. **P* < 0.05.

Eosinophil Chemotactic Response to S1P

FTY720 inhibits T cell emigration through inhibition of S1P–S1P1 signaling.²⁷ Therefore, as readout of S1P1 function on eosinophils, we evaluated the chemotactic response to S1P. The cells were isolated from the bone marrow of IL-5 transgenic mice that were treated with FTY720. Chemotaxis assay using transwells showed that naive T cells had a good chemotactic response to S1P, which was ablated by FTY720 as reported previously.^{12,21} Eosinophils had a significant chemotactic response to S1P but lost the ability to respond to S1P when mice were pretreated with FTY720 (Figure 6A). Similar inhibition of eosinophil chemotaxis to S1P was observed with SEW2871 (Figure 6B). The chemotactic response to stromal-cell derived factor-1 was not affected by the administration of FTY720 or SEW2871 (Figure 6). These data suggest that the migration of eosinophils toward S1P is highly dependent on S1P1.

Discussion

Our study demonstrated that the administration of FTY720 before the final challenge decreased the number of skin-infiltrating eosinophils and the cutaneous late-phase reaction. The egress of eosinophils from the bone marrow was inhibited by FTY720 treatment. This may subsequently lead to attenuate the accumulation of eosinophils in the skin.

By acting as an agonist for S1P receptors and thereby inhibiting lymphocyte egress from lymphoid organs, it has been reported that FTY720 shows a strong therapeutic potential for preventing the rejection of transplanted organs and for treating autoimmune diseases, such as autoimmune encephalomyelitis and systemic lupus ery-

thematosis.²⁸ In fact, some of these possible therapeutic uses are currently being clinically evaluated.²⁹ We have demonstrated that FTY720 impairs naive T cell circulation and markedly disrupts the acquired skin Th1 type immune response.¹² Consequently, FTY720 may have the potential to prevent the onset of disease rather than to treat memory T cell-mediated acquired skin immune responses.¹²

It remains unclear from this study how S1P-S1P receptor signaling participate in the infiltration of eosinophils from the blood to the skin. Several possible mechanisms for the regulation of eosinophil trafficking into the skin can be proposed. First, FTY720 might directly inhibit the migration of eosinophil toward the skin constituents, because eosinophils express S1P1, and S1P is induced at the epidermis of the skin.^{30,31} This idea is supported by the results of our chemotaxis assay, which showed a direct suppressive effect of FTY720 on eosinophil migration toward S1P. Second, a significant reduction of the eosinophilic inflammation in the skin was observed with FTY720, suggesting that the decrease in circulating eosinophils may affect the eosinophil recruitment process. Indeed, FTY720 enhanced the accumulation of adaptively transferred eosinophils in the bone marrow, indicating that eosinophil retention in this organ is also regulated by S1P.

Eosinophils play a key role in the development of cutaneous late-phase reactions. Circulating eosinophils are complemented from the bone marrow in an S1P-S1P1-dependent manner. Previous studies have reported that a decrease in S1P release by sphingosine kinase inhibitors controls a mouse asthmatic model. The authors demonstrated that inhaled delivery of sphingosine kinase inhibitors prevented eosinophilic inflammations and goblet hyperplasia induced by OVA administration.³² Their observation and our finding provide a possibility that FTY720 may be a candidate of treatment modalities for eosinophilic cutaneous inflammations, such as atopic dermatitis, hypereosinophilic syndrome, and Churg-Strauss syndrome.^{33,34}

There have been few studies on S1P receptor expressions on murine eosinophils and the functional role of S1P1 on eosinophils *in vivo*.^{9,35} Our current study indicated that S1P1 expression was lower in eosinophils than T cells. Therefore, the S1P-S1P1 dependency of eosinophils may be lower than that of T cells, which might explain the less inhibitory effects of FTY720 on eosinophils in the blood. In the model where mice were repeatedly challenged with a hapten, FTY720 also reduced the number of skin-infiltrating eosinophils but not T cells. Consequently, FTY720 attenuated the late-phase reaction along with a reduction of eosinophil infiltration. S1P1 is known to be required for normal B cell development.³⁶ S1P4 signaling in migratory response of murine T cells toward S1P remains controversial.^{37,38} In contrast to S1P1 and S1P4 in B and T cells, the roles of these receptors for eosinophils remain unclear. In human, the eosinophil recruitment process has been reported to depend on not only S1P1 but also S1P2 and S1P3 mRNA levels.³⁵ Although we cannot rule out a possibility that the localization of eosinophils is related to S1P3, our *in vivo*

and *in vitro* studies using SEW2871 and FTY720 strongly suggest that S1P1 is involved in bone marrow egress and peripheral tissue localization of eosinophils.

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Camouflage for patients with vitiligo vulgaris improved their quality of life

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Summary

Background Cosmetic camouflage is important for patients with vitiligo vulgaris. However, few studies have investigated its benefit for vitiligo patients.

Objectives To analyze the psychological effects on patients with vitiligo vulgaris by camouflage lessons performed in vitiligo clinics in Kyoto University Hospital and Fukui Red Cross Hospital, Dermatological Life Quality Index (DLQI) questionnaires were collected before and 1 month after camouflage lessons.

Patients Patients with vitiligo vulgaris, who visited our clinics in 2008 and had never experienced camouflage, were enrolled in this study. They took camouflage lessons and continued subsequent self-camouflage for 1 month. Control patients took no lessons and no camouflage.

Results Camouflage improved the scores of DLQI when compared with those without camouflage ($P = 0.005$). Camouflage improved DLQI scores from 5.90 to 4.48. In DLQI subcategories, camouflage lessons improved a subcategory of "symptoms and feelings" ($P = 0.0037$).

Conclusions These data supported the idea that camouflage for patients with vitiligo not only covers the white patches but also improves their quality of life.

Keywords: camouflage, cosmetics, Dermatological Life Quality Index, quality of life, vitiligo

Introduction

Cosmetic camouflage is important for the patients with vitiligo vulgaris, especially when the face, neck, and hands are affected. Cosmetics can give excellent results when they are applied properly.¹ Our vitiligo clinics in Kyoto University and Fukui Red Cross Hospital experienced over 200 patients complaining of "loss of skin color" and provided them camouflage lessons to cover their skin lesions.² However, few reports supported the

evidence that camouflage can improve quality of life (QOL) of vitiligo patients. In addition, psychological effects on Japanese patients with vitiligo have not been evaluated.

Previous studies have demonstrated that camouflage can result in improvement of QOL in patients with pigmentary disorders, scars, and vascular disorders.^{3,4} However, these studies evaluated the effects of camouflage on patients including various skin disorders. As for vitiligo, one report investigated effects of camouflage on vitiligo patients, however patients were limited to Caucasian.⁴ In this article, we evaluated the psychological impact of camouflage on Japanese patients with vitiligo through a questionnaire using Dermatological Life Quality Index (DLQI).

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Methods

Study subjects

The target population in the present study included 202 patients complaining of "loss of skin color," who visited two Vitiligo Clinics located in Kyoto and Fukui, Japan.¹ The number of patients with vitiligo vulgaris was 144. Participation was limited to patients who visited our vitiligo clinics in 2008 and had never experienced camouflage for their skin lesions. The enrolled patients agreed to complete a self-administered questionnaire before and 1 month after camouflage lessons. They continued to use cosmetics by themselves to cover their vitiligo for 1 month after the lessons. Patients who had already taken cosmetic lectures were excluded. Questionnaires were collected both before and 1 month after a camouflage lesson. Eleven patients with vitiligo vulgaris, who refused to take camouflage lessons and had never experienced camouflage for their vitiligo, were enrolled as a control group. They used no cosmetics to cover their lesions during this study. The control patients answered questionnaires at their first visit to our clinics (baseline) and 1 month after the baseline. The institutional medical ethics boards of Kyoto University and Fukui Red Cross Hospital have approved this study, which was conducted according to the principles expressed in the Declaration of Helsinki.

Camouflage lessons

We provided camouflage lessons bimonthly in Vitiligo Clinics in Kyoto University Hospital and Fukui Red Cross Hospital. Lessons were staffed by volunteered specialists for camouflage for pigmentary disorders sent from Non-Profit Organization Medical Makeup Association and Shiseido CO., LTD in Kyoto and Non-Profit Organization Medical Makeup Association in Fukui. The lesson was one-to-one out of regard for patients' sense of shame. During the lesson, patients knew the precise procedure of camouflage and selected a matched skin color based on each patient's condition. Previously reported tips for camouflage were also introduced to them.^{6,7} Cosmetics used for camouflage lessons were Covermark Original (GRAFA Laboratories, Osaka, Japan) and Perfect Cover Foundation VV (Shiseido CO., LTD, Tokyo, Japan). The cosmetics were provided free of charge to the participants.

Data collection

Data regarding patient age, gender, and the distribution of lesions were derived from medical records.

Information regarding the scores of DLQI was derived from a self-administered questionnaire. The Japanese version of DLQI has the same validity and reliability as an original version.^{8,9}

The main variables evaluated were the enrollment of the camouflage lessons and subsequent improvement of DLQI scores. In the present study, DLQI was assessed twice, that is, first at baseline (before a camouflage lesson) and second 1 month after baseline.

Statistical methods

To evaluate the relationship between the enrollment of camouflage lessons and changes of DLQI scores, Student's *t*-test was performed. Assessment of result robustness was carried out by another analysis, in which we eliminated patients who had the exposed vitiligo lesions. Student's *t*-test and Fischer's exact test were also used to examine the characteristics. All analyses were performed using STATA version 9.2 (StataCorp LP, College Station, TX, USA).

Results

Characteristics classified by the enrollment of cosmetic lectures

The characteristics of enrolled patients with vitiligo before and after camouflage lessons are summarized in Table 1. Patient age, duration of disease, and patient gender showed no significant difference between the two groups with or without camouflage lessons. The rate of presence of exposed lesions was higher in patients having camouflage lessons than those without lessons.

Camouflage improved total DLQI scores

Dermatological Life Quality Index scores of patients with camouflage were improved from 5.90 to 4.48. On the contrary, those of patients without camouflage changed from 3.18 to 4.36. The change by camouflage had a statistical significance when compared with that of patients without camouflage ($P < 0.005$; Fig. 1). When patients without exposed lesions were excluded ($n = 27$), camouflage revealed still associated with improvement of DLQI scores ($P = 0.01$) (data not shown).

Camouflage improved "symptoms and feelings" in the DLQI subcategories

In six DLQI subcategories, patients with camouflage showed improvement in "symptoms and feelings" when

Table 1 Characteristics classified by the enrollment of cosmetic lectures

	With camouflage lessons (n = 21)	Without camouflage lessons (n = 11)	P-value
Patient age, duration of disease (months)	48.1 (19.5)	40.8 (17.5)	0.30
Patient gender, % male	52.4	54.5	1.00
Presence of exposed lesions, %	95.2	63.6	0.04
DLQI scores, at baseline	5.90	3.18	0.04
DLQI scores, 1 month after baseline	4.48	4.36	0.93

Values represent sample mean (SDs).

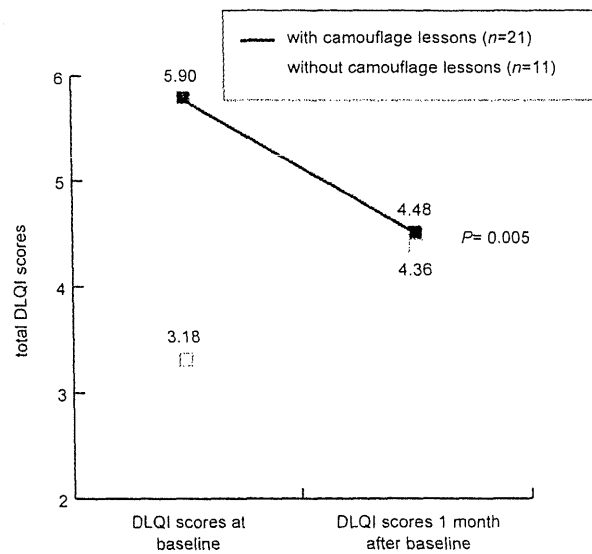


Figure 1 Total DLQI scores of vitiligo patients with or without camouflage.

compared with that of patients without camouflage (Fig. 2). The other five categories exhibited no statistical significance regardless of camouflage (Table 2).

Discussion

Vitiligo vulgaris has profound psychological and social effects on the sufferers, although it is nonlethal. Studies have shown that patients with vitiligo may have low self-esteem and poor body image, experience discrimination from others, and feel stigmatized, resulting in impairment of QOL.^{10–13} In addition, various available medical therapies for vitiligo often fall short of patients' expectations.^{14,15} Therefore, camouflage can be

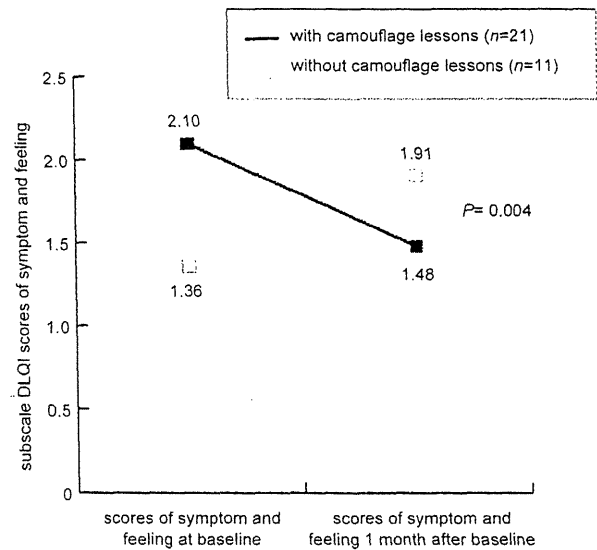


Figure 2 Scores of "symptoms and feelings" of vitiligo patients with or without camouflage.

Table 2 Changes of subscale DLQI scores

	With camouflage lessons (n = 21)	Without camouflage lessons (n = 11)	P-value
Symptom and feeling	−0.62 (1.12)	0.55 (0.69)	0.004
Daily activities	−0.38 (1.47)	0.27 (0.79)	0.18
Leisure	−0.14 (0.65)	0.18 (0.60)	0.18
Work and school	0.05 (0.38)	0.18 (0.40)	0.36
Personal relationships	0.00 (0.55)	0.00 (0.00)	1.00
Treatment	−0.33 (1.02)	0.00 (0.00)	0.29

Values represent sample mean (SD).

recommended when patients are not motivated to treat their diseases or when these therapies do not achieve the expected results. Covering the appearance with cosmetics promotes the social and psychological well-being. Several studies have shown that camouflage can improve the QOL of patients with pigmentary disorders and scars.^{3,4} Ongenae *et al.* used DLQI to demonstrate that camouflage improves the QOL of Caucasian patients with vitiligo with higher DLQI scores or self-assessed disease severity.⁵ Unfortunately, no studies have been conducted in Asian patients with pigmentary disorders. This article is the first report describing the importance of camouflage lessons and camouflage for Japanese patients with vitiligo vulgaris through DLQI. As a limitation of this research, the control group might have a pessimistic rationale, because they refused to take

camouflage lessons. This fact might reflect a frame of mind that differed from those of the patients, who were willing to take lessons.

In our Vitiligo Clinics, patient education is inevitably required to obtain a suitable effect. We provided enough information and techniques to patients with vitiligo vulgaris. We believe that the attitude resulted in improvement of QOL of our vitiligo patients. This paper established evidence that patient education through camouflage lessons is effective for Japanese patients with vitiligo vulgaris. We really hope that camouflage lessons can be available for all patients with vitiligo in the future.

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Keeping vulnerable elderly patients free from pressure ulcer is associated with high caregiver burden in informal caregivers

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Keywords

aging, caregiver burden, home care, informal caregivers, pressure ulcer, vulnerable populations

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Abstract

Rationale and objectives The effect of the presence of pressure ulcers on burden of caregivers is unknown. We investigated the relationship between the state of pressure ulcers in vulnerable elderly patients and the burden on their informal caregivers.

Methods This cross-sectional study enrolled 137 patients aged ≥ 40 years with limited activity and mobility at 10 home care service facilities in Japan. We assessed pressure ulcer status from medical records and caregiver burden using scores from both the Burden Index of Caregivers (BIC) and the Japanese short version of the Zarit Burden Interview (ZBI).

Results Among patients, mean age was 80.9 years, 31.4% were men, and 83.9% were free from pressure ulcers. Multivariable analysis showed that caregivers whose patients were free from pressure ulcers had significantly higher caregiver burden as assessed by both the BIC [β -coefficient = 3.18, 95% confidence interval (CI): 1.42–4.95, $P = 0.003$] and ZBI scores (β -coefficient = 1.94; 95%CI = 0.30–3.58; $P = 0.03$).

Conclusions Our results suggest that the continuous effort involved in keeping patients free from pressure ulcers may be associated with high caregiver burden in informal caregivers.

Introduction

The number of elderly patients requiring care is increasing in many countries as a development of the aging of society. In the UK, the number of people aged over 65 with various chronic diseases and disabilities is projected to increase two- to three-fold in the next 70 years [1]. Of these, a considerable number of bedridden patients have been provided care at home by their families, namely 'informal caregivers'. A recent report suggested that a higher burden on informal caregivers was associated with

risk of death: caregivers experiencing caregiver strain had mortality risks that were 63% higher than non-caregiving controls [2].

Several studies have revealed relationships between the burden of care and social characteristics in several disease-specific populations [3–5]. Caregiver burden was defined by Zarit as the extent to which caregivers perceived that their emotional or physical health, social life and financial status suffered as a result of caring for their relative [6]. Therefore, caregiver burden must be measured from various aspects aimed at revealing the

multidimensional relationship between caregiver burden and the health status of both caregivers and their patients [7,8].

To date, however, no studies have examined the relationship between diseases or symptoms commonly observed in vulnerable elderly patients, such as aspiration pneumonia and pressure ulcer, and their burden of care. In particular, pressure ulcer is a significant health problem among vulnerable elderly patients mainly due to increased morbidity, increased health-related costs and reduced patient quality of life [9,10]. In home care settings, pressure ulcers appear a more serious problem because informal caregivers are continuously required to prevent them [11,12]. It is therefore worthwhile to quantitatively ascertain the caregiver burden of vulnerable patients with a higher risk of pressure ulcer.

Here, we investigated the relationship between the state of pressure ulcer in vulnerable elderly patients and the burden of care as assessed using scores from both the Burden Index of Caregivers (BIC) and the short version of the Japanese version of the Zarit Burden Interview (ZBI), based on data from a multicenter survey of vulnerable home care patients in Japan.

Methods

Study subjects

The target population was vulnerable elderly patients in 10 facilities (total $n = 801$) providing home care service in Kyoto, Japan. Participation was limited to patients showing limitations in activity and mobility (score for either of 1 or 2 in the Braden scale) and those who received care at home from related informal caregivers [13]. Those who became patients due to attempted suicide were excluded on the basis that their burden of care was considered to differ from those of other patients. Participants were recruited in accordance with these criteria from all patients of the 10 facilities. Patients aged less than 40 years were also eliminated because Japanese care insurance is intended for those aged 40 years or more. The study was approved by the institutional review board of Kyoto University, Kyoto, Japan.

Pressure ulcer assessment

The main variables evaluated were the state of pressure ulcer and the degree of caregiver burden. In the present study, information about pressure ulcers was derived from medical records. We defined the presence of pressure ulcer according to the pressure ulcer staging system of the National Pressure Ulcer Advisory Panel and included those categorized as Stage II or worse, representing at least a partial-thickness loss of the dermis [14]. Care need was evaluated according to the national index of long-term care need on a 6-point Likert scale derived from questionnaires regarding various aspects of patient health, including daily activity, episodes of incontinence, and nutritional status [15]. To estimate Japanese care insurance needs, the index was ultimately determined by the patient's local municipal review board of home care experts, including doctors, nurses and care workers.

Caregiver burden measurement

In the present study, a caregiver was defined as a person having a familial relationship with a patient and who most frequently

provided informal care in each family. Caregiver burden was assessed using the BIC, a recently developed 11-item multidimensional questionnaire validated against the Short Form-8 (SF-8) and ZBI which is considered highly reliable among caregivers providing home health care to patients with various conditions [8]. SF-8 is a short form of the health-related quality of life scale SF-36, and the ZBI is a 22-item care burden scale in frequent use throughout the world. The BIC has two novel domains, 'service-related burden' and 'existential burden', in addition to ordinary concepts about burden of care, and is designed to enable the precise measurement of the particular circumstances of Japanese care settings. Another advantage of the BIC is that its small number of items is not considered burdensome to respondents, in contrast to most other scales which have more items than BIC [7,16]. For both the BIC and ZBI, higher scores represent greater caregiver burden.

Statistical methods

The relationship between the state of a pressure ulcer and BIC score was examined using multivariable linear regression analysis. Models were adjusted for patient age, patient gender, caregiver age, caregiver gender, family relationship, daily estimated time for caregiving, national index of long-term care need, presence of Alzheimer-type dementia, and history of violence by patients within past 3 months.

Additionally, to assess the robustness of our results, we used the short version of the Japanese version of the ZBI, an eight-item questionnaire validated with the full version of the ZBI. Multivariable linear regression was also employed to compare with the state of pressure ulcers and ZBI score, adjusted for the same possible confounders as mentioned above [16,17].

Furthermore, subgroup analysis was performed in patients free from pressure ulcers. Multivariable linear regression analysis was used to examine the relationship between airmat use and BIC score, with adjustment for the same possible confounders mentioned above.

A multiple imputation approach using a chained equations method was employed to account for missing items of the BIC, ZBI and other confounding factors [18,19]. Among the total data, 0.9% of BIC items, 0.6% of ZBI items and 1.3% of confounders had missing values. Student's *t*-test was used for all other univariate analyses. Linear regression models took into account cluster effects at the facility level. All analyses were performed using STATA version 9.2 (StataCorp LP, College Station, TX, USA).

Results

Of 178 patients who fulfilled the inclusion criteria, 28 declined enrolment and 13 agreed but did not complete the questionnaire, leaving 137 patients (77.0%) finally included in the present study. Table 1 shows patients and caregivers characteristics, categorized by the state of pressure ulcer. The 137 patients had a mean age of 80.9 years, 31.4% were men, and 83.9% were free from pressure ulcer. Caregivers had a mean age of 65.0 years, 29.2% were men, and the mean duration of caregiving was 6.58 years.

Table 1 Baseline patient and caregiver characteristics classified by the state of pressure ulcer. Values represent sample means (SDs)

Characteristic	Patients free from pressure ulcer (<i>n</i> = 115)	Patients with pressure ulcer (<i>n</i> = 22)
Patient age, years (SD)	80.9 (11.3)	80.8 (13.6)
Patient gender, male, %	33.0	32.7
Caregiver age, years (SD)	65.4 (10.5)	62.6 (9.3)
Caregiver gender, male, %	25.2	50.0
Family relationship, caregiving spouse, %	38.3	27.3
Family relationship, caregiving parents, %	46.1	63.6
Daily estimated time for caregiving, hours (SD)	7.34 (5.55)	7.49 (5.68)
National index of long-term care need, grade (SD)	4.42 (0.91)	4.50 (0.96)
Neurodegenerative disorder, %	13.1	18.2
Alzheimer-type dementia, %	13.0	22.7
Violence by patients within past 3 months	6.71	13.6

Table 2 Factors associated with total Burden Index of Caregivers score using a multivariable linear regression model (*n* = 137)

Characteristic	β -coefficient	95% confidence interval	<i>P</i> -value
Free from pressure ulcer (vs. with pressure ulcer)	3.18	1.42 to 4.95	0.003
Patient age, per 1-year increase	-0.02	-0.16 to 0.12	0.72
Patient gender, female (vs. male)	0.42	-4.69 to 4.78	0.98
Caregiver age, per 1-year increase	-0.09	-0.24 to 0.22	0.93
Caregiver gender, female (vs. male)	-0.02	-2.78 to 2.74	0.99
Family relationship, spouse (vs. others)	1.56	-4.08 to 7.20	0.54
Daily estimated time for caregiving, per 10-hour increase	0.56	-1.23 to 2.34	0.54
National index of long-term care need, the severest grade (vs. other grades)	-1.58	-3.50 to 0.34	0.09
Alzheimer-type dementia (vs. no)	2.12	-3.95 to 8.18	0.44
Violence by patients within past 3 months (vs. no)	7.15	4.45 to 9.84	<0.001

Relationship between the state of pressure ulcer and the care burden of informal caregivers

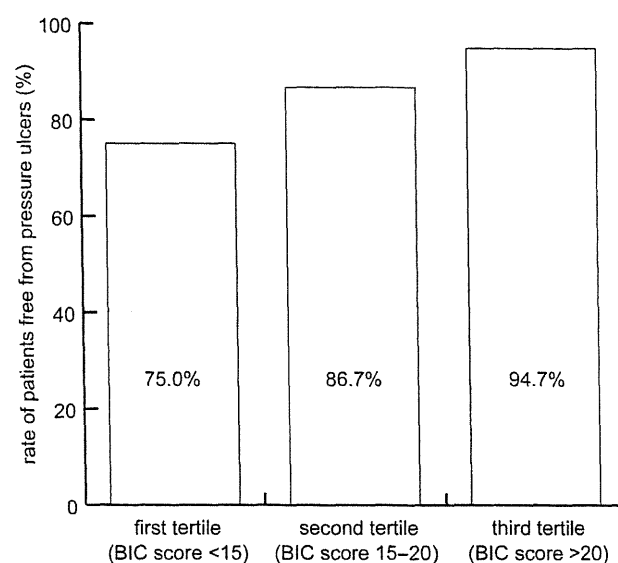
Results for total BIC score were 14.2 and 17.9 for those with pressure ulcer and those who were free from pressure ulcer respectively. Figure 1 shows the rate of patients who were free from pressure ulcers, categorized into tertiles by BIC score, indicating a dose-dependant relationship between the state of pressure ulcers and caregiver burden.

In multivariate analysis, caregivers whose patients were free from pressure ulcer had significantly higher BIC scores than those of patients with pressure ulcer [β -coefficient = 3.18, 95% confidence interval (CI): 1.42–4.95, P = 0.003] (Table 2).

With regard to the ZBI as the scale of caregiver burden, multivariable analysis revealed that caregivers whose patients were free from pressure ulcer were likely to have a higher ZBI score (β -coefficient = 1.94, 95%CI: 0.30–3.58, P = 0.03).

Subgroup analysis

After excluding patients with pressure ulcers (*n* = 115), results for total BIC score were 19.2 and 16.8 with and without airmat use respectively. Multivariate analysis showed that caregivers who prepared airmats for their patients had significantly higher BIC

**Figure 1** The rate of patients free from pressure ulcers in each sub-group categorized according to tertiles of the Burden Index of Caregivers (BIC) score.

Characteristic	β -coefficient	95% confidence interval	P-value
Usage of airmat (vs. no)	3.52	1.10 to 5.95	0.01
Patient age, per 1-year increase	-0.04	-0.18 to 0.09	0.47
Patient gender, female (vs. male)	0.70	-4.50 to 5.91	0.76
Caregiver age, per 1-year increase	-0.02	-0.27 to 0.24	0.89
Caregiver gender, female (vs. male)	-1.23	-4.60 to 2.14	0.42
Family relationship, spouse (vs. others)	1.32	-5.05 to 7.69	0.64
Daily estimated time for caregiving, per 10-hour increase	0.10	-1.80 to 2.00	0.91
National index of long-term care need, the severest grade (vs. other grades)	-3.42	-5.96 to -0.88	0.02
Alzheimer-type dementia (vs. no)	3.10	-5.29 to 11.49	0.42
Violence by patients within past 3 months, (vs. no)	6.84	3.62 to 10.07	0.001

Table 3 Factors associated with total Burden Index of Caregivers score in limited patients who were free from pressure ulcers, using a multivariable linear regression model ($n = 115$)

scores than those who did not (β -coefficient = 3.52, 95%CI: 1.10–5.95, $P = 0.01$). In contrast, patients with the severest grade of long-term care need according to the national index were likely to have lower caregiver burden than patients with less severe grades (β -coefficient = -3.42, 95%CI: -5.96 to -0.88, $P = 0.02$) (Table 3).

Discussion

Our present study quantitatively revealed that informal caregivers whose patients were free from pressure ulcer had a higher caregiver burden than those who failed to prevent pressure ulcer. Of particular note, these results were derived using two validated scales of caregiver burden, the BIC and ZBI, confirming the robustness and reliability of the observed relationship. The association also tended to be clearly defined in analyses using categorized BIC scores, and the rate of patients who were free from pressure ulcers increased with increasing BIC score in a dose-dependent manner.

The participants in the present study were vulnerable and mostly bedridden, suggesting that they had a high risk of developing pressure ulcer [20]. This observed relationship therefore indicates an association between efforts to prevent pressure ulcer and higher caregiver burden. The difference in BIC score, categorized by the state of pressure ulcer, is shown in Table 2. Comparing the difference with other factors, a BIC score of 3.18 was almost six times larger than that from spending an additional 10 hours for home care per day. Preventing pressure ulcer is not only a time-consuming burden but also hard work which requires the knowledge and ability to carry out prevention protocols for informal caregivers [12,20]. Given the strong emphasis placed on the responsibility of caregivers in preventing pressure ulcer in Japan, it seems natural that caregivers who try to prevent pressure ulcer feel a higher degree of strain [21]. Furthermore, subgroup analysis showed a relationship between airmat use and relatively high burden in caregivers whose patients were free from pressure ulcers. All patients in the present study had severely limited activity and mobility, making them candidates for airmat use. Caregivers who prepared airmats for patients before development of pressure ulcers therefore seemed to be more concerned about patient well-being. Results from subgroup analysis indicated that dedicated caregivers were likely to have higher caregiver burden.

These findings potentially raise a conflicting issue in home care settings, given the general acceptance that airmat use reduces caregiver burden [22]. However, caregiver burden is a comprehensive concept which includes not only physical but also psychological burden regarding the 'meaning of caregiving' [8]. Dedicated caregivers are likely to strive not only to care for but also to cure their patients [23]. This attitude may exaggerate the burden with respect to the 'meaning of caregiving', because most vulnerable patients have little chance for recovery. To deal with psychological burden, present efforts to reduce physical burden, such as the introduction of airmat use and home care service, should be complemented by more intensive care towards informal caregivers, including counselling by psychiatric specialists. Home nurses should consider not only patient health but also psychological distress in caregivers. In home care settings, self-administered screening to assess depressive symptoms, such as the short version of the Center for Epidemiological Studies Depression Screening Index, may be feasible [24]. Furthermore, a society-wide paradigm shift from cure to care in managing home care patients appears necessary.

Our results also showed several other factors associated with caregiver burden. A statistically significant relationship was observed between violent behaviour in patients and increased caregiver burden, supporting previous investigations into the association between aggression in patients with Alzheimer-type dementia and caregiver burden [25]. In the subgroup analysis, the severest grade of long-term care need according to the national index was associated with lower caregiver burden. Although not statistically significant, this relationship was also seen in the main analysis. One possible explanation for this relationship may be that less impaired patients might require more continuous care and observation than completely bedridden patients. At the very least, this relationship might imply the intractability of caregiver burden in informal caregivers.

Several limitations of the study warrant mention. First, additional details about pressure ulcers were not ascertained in the medical records, so we were unable to evaluate the influence of other variables in the relationship between pressure ulcer preventing and caregiver burden. Second, we did not investigate the relationship between the preventive status of pressure ulcers and caregiver burden in other countries. Global generalization of our results therefore requires further investigation. Third, the cross-

sectional design of our study prevents us from determining causation or a temporal relationship. As a general limitation of observational studies, adjustment of unknown confounding factors highly associated with the investigated relationships was not possible.

In conclusion, using a multicenter sample of vulnerable patients, our results show that informal caregivers whose patients were free from pressure ulcer are likely to have higher caregiver burden. We interpret our results to mean that the continuous effort required to prevent pressure ulcer might be associated with higher strain in informal caregivers. A society-wide approach towards managing psychological burden in informal caregivers is now necessary.

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各論

アトピー性皮膚炎の 診療スタンダード Up To Date

山本 洋介・松村 由美

- アトピー性皮膚炎治療の基本は？
- 個々の皮疹の重症度に応じ、適切な外用療法を選択することが基本である。
- アトピー性皮膚炎，診療ガイドライン，外用療法

アトピー性皮膚炎は、皮膚の乾燥とバリア機能異常とともに、アレルギー反応が関与することによって生じる疾患である。患者は、各種アレルギー性疾患を合併することが多いため、アレルギーの側面が強調されがちであるが、皮膚の生理学的な異常が本疾患の根幹であるといっても過言ではない。事実、近年、欧米では多くのアトピー性皮膚炎患者において、角層形成に重要な役割を担い、また、その代謝産物が天然保湿因子の主成分であるフィラグリンの遺伝子に変異があることが明らかになり、スキンケアの重要性が分子レベルで示された。すなわち、外用療法によるスキンケアがアトピー性皮膚炎治療の基本である。

本邦では、2000年に日本皮膚科学会による「アトピー性皮膚炎治療ガイドライン」が策定された。その後、2008年には診断基準・重症度分類・治療ガイドラインを包含した「アトピー性皮膚炎診療ガイドライン」へと発展し、2009年に改訂され現在に至っている。また別に、厚生労働省免疫アレルギー疾病予防・治療研究推進事業による「アトピー性皮膚炎治療ガイドライン2008」も存在するが、両者の間で差異はあるものの大きく矛盾する記述はない。本稿では、日本皮膚科学会において2008年・2009年に策定された版に関して、診断面・治療面を中心にその概要を述べることとする。

アトピー性皮膚炎の定義

本疾患の定義は1994年に策定、2008年に改訂された「アトピー性皮膚炎の定義・診断基準」による(表1)。すなわち「アトピー性皮膚炎は、増悪・寛解を繰り返す、瘙痒のある湿疹を主病変とする疾患であり、その患者の多くはアトピー素因をもつ」とされている。この場合、アトピー素因とは「①気管支喘息、アレルギー性鼻炎・結膜炎、アトピー性皮膚炎のいずれかの疾患に対する家族歴・既往歴を有すること」、または「②IgE抗体を産生しやすい素因があること」を指す。

アトピー性皮膚炎の診断

基本項目として「①瘙痒があること、②左右対称性の分布をとり、眼周・口周・四肢関節部などに好発する特徴的な湿疹病変であること、③慢性の経過をとり、増悪・寛解を繰り返すこと」、以上3つを満たすものを、症状の重症度には関係なくアトピー性皮膚炎と診断する。なお、慢性の経過とは、乳児では2カ月以上、その他では6カ月以上の持続するものを指す。

上記3項目を完全に満たさないものの、アトピー性皮膚炎が疑われる症例は、急性ないし慢性

