A novel JAK inhibitor JTE-052 reduces skin inflammation and ameliorates chronic dermatitis in rodent models: Comparison with conventional therapeutic agents

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**Abstract**

Janus kinases (JAKs) are required for several inflammatory cytokine signalling pathways and are implicated in the pathogenesis of chronic dermatitis, including atopic dermatitis and psoriasis. JAK inhibitors are therefore promising therapeutic candidates for chronic dermatitis. In this study, we evaluated the effects of the novel JAK inhibitor JTE-052 on inflammatory responses associated with chronic dermatitis, and compared its profile with those of conventional therapeutic agents in rodent models of chronic dermatitis. JTE-052 inhibited the Th1-, Th2- and Th17-type inflammatory responses of human T cells and mast cells in vitro. Oral administration of JTE-052 inhibited skin inflammation in hapten-induced chronic dermatitis in mice, associated with reduced levels of inflammatory cytokines in the skin and immunoglobulin (Ig) E in serum. In contrast, although ciclosporin partly inhibited skin inflammation, it did not reduce interleukin (IL)-4 production in skin, and enhanced IgE production in serum. Oral administration of JTE-052 also inhibited skin inflammation in mouse models of atopic dermatitis and psoriasis induced by a mite extract, thymic stromal lymphopoietin or IL-23. The maximal efficacy of JTE-052 in these dermatitis models was superior to the conventional therapeutic agents, ciclosporin and methotrexate. Topical application of JTE-052 ointment ameliorated hapten-induced chronic dermatitis in rats more effectively than tacrolimus ointment. Furthermore, JTE-052 ointment did not cause the thinning of normal skin associated with topical corticosteroids. These results indicate that JTE-052 is a promising candidate as an anti-inflammatory drug for various types of chronic dermatitis, with a distinctly different profile from conventional therapy following either oral or topical application.

**Keywords**
atopic dermatitis, corticosteroids, cytokine signalling, immunosuppressants, psoriasis
1 INTRODUCTION

Atopic dermatitis (AD) and psoriasis are the most common chronic inflammatory skin diseases. They are characterised pathophysiological by disrupted skin homeostasis and dysregulated immune response. Several medications are used to treat these diseases with the aim of reducing skin inflammation. Topical steroids and topical immunosuppressants are the main agents used for chronic dermatitis, and show definite therapeutic effects; however, their value is limited by local side effects and insufficient efficacy. Oral steroids or immunosuppressants such as methotrexate and ciclosporin may also be used in patients with moderate-to-severe symptoms, but their usage is limited by systemic side effects. Novel therapies with fewer side effects are therefore needed for the effective treatment of chronic dermatitis.

Biologics such as anti-tumor necrosis factor (TNF) monoclonal antibody, ustekinumab and secukinumab, which have been approved for psoriasis, and dupilumab, which is under development for AD, have recently shown impressive results with good efficacy in clinical trials. These trials suggested that inhibition of inflammatory cytokine signal transduction may offer a promising approach to the treatment of chronic dermatitis. Janus kinases (JAKs) comprise a non-receptor-type tyrosine kinase family composed of four enzymes (JAK1, JAK2, JAK3 and Tyk2), which transduce signals from multiple type I and type II cytokine receptors and mediate various inflammatory responses. Various JAK-related cytokines play roles in the pathophysiology of psoriasis (interleukin (IL)-12, IL-23, IL-22) and AD (IL-4, IL-13, IL-31, thymic stromal lymphopoietin (TSLP)). Inhibition of JAKs may therefore represent a novel therapeutic approach for chronic dermatitis. Indeed, clinical trials of JAK inhibitors in patients with chronic dermatitis have already demonstrated definite effectiveness. Furthermore, a preclinical study also reported efficacy of a JAK inhibitor in animal models of chronic dermatitis. However, the difference between conventional therapies and JAK inhibitors has not been fully investigated.

We recently developed a novel JAK inhibitor, JTE-052, that was shown to be orally active and more potent than tofacitinib in mice. In this study, we investigated the efficacy of oral JTE-052 in several rodent models of chronic dermatitis, and compared its profile with conventional therapeutic agents. We also investigated the efficacy of topical application of JTE-052 ointment in chronic dermatitis model, in the light of the likely reduced risk of systemic side effects of this mode of application.

2 MATERIALS AND METHODS

2.1 Animals

Balb/c mice were obtained from Japan SLC, Inc. (Hamamatsu, Japan). C57BL/6 mice, Nc/Nga mice and BN rats were obtained from Charles River Japan, Inc. (Yokohama, Japan). Animals were maintained under specific pathogen-free conditions at a room temperature of 23±3°C and air humidity of 55±15% with a 12-h/12-h light/dark cycle. All procedures related to the use of animals in this study were reviewed and approved by the Institutional Animal Care and Use Committee of Japan Tobacco Inc.

2.2 Compounds

JTE-052 was synthesised at the Central Pharmaceutical Research Institute, Japan Tobacco Inc. (Osaka, Japan). JTE-052 inhibited JAK1, JAK2, JAK3 and Tyk2 with IC50 values of 2.8, 2.6, 13 and 58 nM, respectively, in enzyme assays, and inhibited IL-2, IL-6, IL-23, IFN-α and GM-CSF signalling in analogy with other JAK inhibitors such as tofacitinib in cellular assays. Ciclosporin was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Methotrexate hydrate was purchased from Sigma-Aldrich (St. Louis, MO, USA). Tacrolimus ointment 0.1% (protopic) and difluprednate ointment 0.05% (Myser) were purchased from Astellas Pharma Inc. (Tokyo, Japan) and Mitsubishi Tanabe Pharma Corporation (Osaka, Japan), respectively. For the in vitro experiments, JTE-052 was dissolved in dimethyl sulfoxide and diluted with the buffer used in each experiment. For the in vivo experiments, JTE-052, ciclosporin and methotrexate were suspended in 0.5% (w/v) methylcellulose solution for oral administration or dispersed in petrolatum-based ointment for topical administration.

2.3 Cellular assay

Human peripheral blood was obtained from healthy volunteers with informed consent, based on the Declaration of Helsinki. Human memory CD4+ T cells were isolated from peripheral blood using Lymphoprep™ and a human memory CD4+ T cell isolation kit (Miltenyi Biotec Inc., Bergisch Gladbach, Germany). For determination of cytokine production by memory CD4+ T cells, human memory CD4+ T cells were plated at 1×105 cells/well in 96-well plates coated with 3 μg/mL anti-CD3 antibody (Affymetrix, Inc., Santa Clara, CA, USA) with 3 μg/mL soluble anti-CD28 (BD Biosciences, San Jose, CA, USA) in the presence or absence of JTE-052 for 3 days. The supernatant was collected, and IL-4, IL-13, interferon (IFN)-γ, IL-17 and IL-22 were measured by ProcartaPlex Multiplex Immunoassays (Affymetrix, Inc.). Human mast cells were obtained from CD34+ cord blood cells (Lonza Walkersville Inc., Walkersville, MD, USA) by culture in the presence of stem cell factor, IL-6 and IL-3 for 10 days, followed by stem cell factor and IL-6 for 8 weeks. For determination of IL-13 production by mast cells, human mast cells were plated in 96-well plates at 2×105 cells/well in the presence or absence of JTE-052. Following preincubation with the compound for 10 minutes, the cells were stimulated by adding 10 ng/mL recombinant human IL-4 and 1 μg/mL immunoglobulin (lg) E for 5 days. The cells were then replated at 1.2×105 cells/well, and cultured with 1 μg/mL anti-IgE for an additional 5 hours. The supernatants were collected, and IL-13 was measured by enzyme-linked immunosorbent assay (ELISA) (GEN-Probe Inc., San Diego, CA, USA).

2.4 Hapten-induced chronic dermatitis in mice

Hapten-induced chronic dermatitis was induced in female BALB/c mice as described previously. Briefly, mouse ears were treated with 25 μL of 0.15% 2, 4-dinitrofluorobenzene (DNFB) dissolved in acetone/olive oil (3:1) once a week for 5 weeks. Ear thickness as an index of ear swelling was measured with a digital thickness gauge (Digimatic Indicator;
Mitutoyo Corporation, Kawasaki, Japan) before and 24 hours after DNFB application, and expressed as the increase in thickness from the baseline measurement. JTE-052 and ciclosporin were administered orally once a day from the day of first DNFB application. After the last measurement of ear thickness, mice were anesthetised, and blood samples were collected. The mice were then euthanised, and their ears were excised for analysis of cytokine expression and histological evaluation. Serum total IgE and anti-2,4-dinitrophenol (DNP)-specific IgE levels were assessed by ELISA (Shibayagi Co., Ltd., Shibukawa, Japan).[22]

Ear sections were homogenised, and cytokine levels in the supernatant were assessed by ELISA (R&D Systems, Inc., Minneapolis, MN, USA).

2.5 | Mite extract- and cytokine-induced dermatitis model in mice

Mite extract-induced dermatitis was induced in female Nc/Nga mice as described previously.[23] Briefly, 5 μg of Dermatophagoides pteronyssinus extract (Cosmo Bio Co. Ltd., Tokyo, Japan) was injected intradermally in the ears of mice three times a week for 3 weeks, and ear thickness was measured 24 hours later. TSLP-induced dermatitis was induced in female C57BL/6 mice as described previously[18] with minor modifications. Briefly, 0.5 μg of recombinant mouse TSLP (R&D Systems, Inc.) was injected intradermally in the ears of mice on days 1, 3, 5, 8 and 10, and ear thickness was measured 24 hours after each injection. IL-23-induced dermatitis was induced in female C57BL/6 mice as described previously[24] with minor modifications. Briefly, 0.25 μg of recombinant mouse IL-23 (R&D Systems, Inc.) was injected intradermally in the ears of mice on days 1, 3, 5, 8 and 10, and ear thickness was measured on days 1, 3, 5, 8, 10 and 12. In each model, JTE-052, ciclosporin and methotrexate, respectively, were administered orally from the day of the first injection.

2.6 | Hapten-induced chronic dermatitis model in Rat

Hapten-induced chronic dermatitis was induced in male DN rats as described previously[25] with minor modifications. Briefly, rat ears were treated with 30 μL of 0.5% 2,4-dinitrochlorobenzene (DNCB) dissolved in acetone/olive oil (4:1) on days 1, 3, 7, 9, 12, 14, 16, 19 and 21. Ear thickness was measured as an index of ear swelling 6 hours after DNCB application, and expressed as the increase in thickness from baseline. JTE-052 ointment, tacrolimus ointment or difluprednate ointment was administered topically once a day from the day of first DNCB application. After the last measurement of ear thickness, rats were euthanised, and their ears were excised for histological evaluation.

2.7 | Statistical analysis

Data are expressed as the mean±standard deviation of the indicated number of samples. The significance of differences between two groups was assessed by Student’s t-tests (for homoscedastic data) or Aspin-Welch t-tests (for heteroscedastic data), after homoscedasticity analysis by F-tests. Differences among multiple groups were analysed by Dunnett’s tests (for homoscedastic data) or Steel’s tests (for heteroscedastic data) after homoscedasticity analysis by Bartlett’s test.

3 | RESULTS

3.1 | JTE-052 inhibits inflammatory responses including Th1-, Th2- and Th17-type responses

Th1, Th2 and Th17-type responses are thought to be involved in several chronic dermal diseases.[14] We therefore used a cell-based assay...
Regarding T cells, anti-CD3/CD28 stimulation increased the Th-type cytokines IFN-γ, IL-4, IL-13, IL-17A and IL-22 in human memory CD4+ T cells after 3 days of incubation, all of which were dose-dependently inhibited by JTE-052 (Figure 1A). We also investigated the inhibitory effect of JTE-052 on Th-related cytokine production in non-T cells. Mast cells have been reported to play an important role in the pathogenesis of allergic diseases by producing Th2-type cytokines. We therefore determined the effect of JTE-052 on mast cells. JTE-052 dose-dependently inhibited IL-13 production from human cord blood-derived mast cells stimulated with IL-4 and IgE/anti-IgE (Figure 1B). These results indicated that JTE-052 inhibited Th1-, Th2- and Th17-type cytokine production from both T cells and non-T cells.

### 3.2 JTE-052 inhibits skin inflammation in hapten-induced chronic dermatitis after oral administration

The repeated hapten-induced chronic dermatitis model is considered to involve Th2 cells and mast cells, and is a useful model of human AD. To determine if JTE-052 reduced skin inflammation in chronic dermatitis, we examined its effect on DNFB-induced chronic dermatitis in mice. Repeated topical application of DNFB to mouse ears induced ear swelling from 24 hours after the second application, and ear thickness increased in proportion to the number of exposures to DNFB. Oral administration of JTE-052 at doses of 0.3-30 mg/kg was well tolerated (even 100 mg/kg was tolerated; data not shown), and inhibited the ear swelling in a dose-dependent manner. Ciclosporin also inhibited the ear swelling at 30 mg/kg (maximal tolerable dose in mice, data not shown). JTE-052 was more effective than 30 mg/kg ciclosporin at doses of 3 and 30 mg/kg (Figure 2A). Histopathologically, acanthosis and spongiosis in the epidermis and infiltration of inflammatory cells in the dermis were observed in DNFB-stimulated, vehicle-treated mice. Oral administration of JTE-052 reduced the severity of the histopathological changes in a dose-dependent manner, while ciclosporin had no effect on any of the histopathological changes (Figure 2B). We investigated inflammatory cell activation in this model by measuring inflammatory cytokine levels in ear skin. IL-4, IL-13 and TNF-α levels were increased in the vehicle-treated group after the fifth application of DNFB. JTE-052 inhibited the increases in all these cytokine levels (Figure 2C). To investigate antibody production, we also determined total IgE levels and "hapten-specific" anti-DNP IgE in the serum after the fifth application of DNFB. Total and anti-DNP IgE were increased in the vehicle group, and JTE-052 inhibited the increase in total and anti-DNP IgE (Figure 2D). Ciclosporin reduced the increases in IL-13 levels in the vehicle group, but JTE-052 was more effective in inhibiting these increases. The results are expressed as mean±standard deviation (n=10). *P<0.05, **P<0.01 vs vehicle by Dunnett’s test. &P<0.05, &&P<0.01 vs vehicle by Steel’s test.

**FIGURE 2** Oral administration of JTE-052 inhibits skin inflammation in hapten-induced chronic dermatitis in mice. Mice received topical application of 0.15% DNFB in acetone/olive oil or vehicle (sham [S]) on the ear once a week for 5 wk. Vehicle (V), JTE-052 (0.3, 3, or 30 mg/kg) or ciclosporin (Cs; 30 mg/kg) was administered orally once daily for 29 d from the day of first DNFB application. (A) Ear thickness was assessed before and 24 h after the fifth DNFB application. Data were expressed as the increase in ear thickness from baseline. (B) Histological analysis at 24 h after the fifth DNFB application. (C) Cytokine expression in ear tissues 4 h (IL-13 and TNF-α) and 24 h (IL-4) after the fifth DNFB application. (D) Total IgE and anti-DNP IgE levels in serum at day 30. The results are expressed as mean±standard deviation (n=10). *P<0.05, **P<0.01 vs vehicle by Dunnett’s test. &P<0.05, &&P<0.01 vs vehicle by Steel’s test.
and TNF-α levels in ear skin but had no effect on IL-4. Moreover, ciclosporin potentiated serum anti-DNP IgE levels in this model, consistent with a previous report.[22]

3.3 | Comparison of efficacies of oral JTE-052 and conventional therapy in AD-like and psoriasis-like dermatitis in mice

We examined the effects of JTE-052 on other chronic dermatitis models related to AD and psoriasis, and compared its efficacy with conventional therapeutic agents used to treat these diseases. Mite extract-induced dermatitis in mice involves AD-like skin lesions and is reported to have an AD-like pathophysiology.[23] TSLP-induced dermatitis is also associated with the pathobiology of AD.[18] We therefore determined the effects of JTE-052 in these AD models. Repeated intradermal injection of mite extract or TSLP in mouse ears increased ear swelling at 24 hours after the second injection, and ear thickness increased in proportion to the number of injections in the vehicle-treated mice. Oral administration of JTE-052 reduced ear swelling in a dose-dependent manner in both AD models, while the conventional agent for severe AD, ciclosporin, showed no clear inhibitory effect even at the maximal tolerated dose of 30 mg/kg in these models (Figure 3A,B). IL-23-induced dermatitis in mice has been reported to have a psoriasis-like pathophysiology,[24] and we therefore investigated the effect of JTE-052 in this model. Repeated intradermal injection of IL-23 in mouse ears caused ear swelling 48 hours after the second injection, and ear thickness increased in proportion to the number of injections. Oral administration of JTE-052 inhibited the ear swelling in a dose-dependent manner (Figure 3C). Methotrexate inhibited the increase in ear thickness at the maximal tolerated dose for mice of 1 mg/kg (data not shown). The efficacy of JTE-052 at doses of 3 and 30 mg/kg was superior to that of 1 mg/kg methotrexate.

3.4 | Topical JTE-052 ointment ameliorates hapten-induced chronic dermatitis in rats

We investigated the effect of topical administration of JTE-052 ointment on skin inflammation in a rat model of chronic dermatitis. Repeated application of DNCB-induced ear swelling from 6 hours after the third application, and ear thickness increased in proportion to the number of exposures to DNCB, reaching a plateau at the seventh application in placebo-treated or non-treated rats. Topical administration of JTE-052 ointment inhibited the increase in ear thickness in a concentration-dependent manner (Figure 4A). Histopathologically, acanthosis and spongiosis in the epidermis and infiltration of inflammatory cells in the dermis were prominently observed in the placebo ointment-treated rats. Topical administration of JTE-052 ointment reduced the severity of the histopathological changes in a dose-dependent manner (Figure 4B). Tacrolimus ointment 0.1% reduced ear thickness and the severity of the histopathological changes in DNCB-induced dermatitis without affecting normal skin thickness. The efficacies of JTE-052 ointment at 0.3% or 3% were superior to tacrolimus ointment 0.1% (Figure 4A,C). Administration of the topical corticosteroid difluprednate ointment 0.05% inhibited DNCB-induced ear swelling (Figure 4C). We also investigated the local side effect of the ointments on normal rat skin. Treatment with JTE-052 ointment 3% for 22 days on the ear had no effect on normal ear thickness. In
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FIGURE 4. Topical application of JTE-052 ointment ameliorates hapten-induced chronic dermatitis in rats. Rats received topical application of 0.5% DNCB in acetone/olive oil or vehicle on the ear three times a week for 3 wk. JTE-052 ointment (placebo, 0.03%, 0.3% or 3%) or tacrolimus ointment (0.12%) was administered topically once daily for 20 d from the day of first DNCB application. (A) Ear thickness was assessed 6 h after DNCB application and expressed as the increase in thickness from baseline. (B) Histological analysis on day 21. (C) Effect of difluprednate ointment 0.05% on hapten-induced chronic dermatitis was determined in a separate experiment. (D) Normal rats were administered topical JTE-052 ointment (placebo, 3%), tacrolimus ointment 0.1% or difluprednate ointment 0.05%, and ear thickness was assessed on day 21. The results are expressed as mean ± standard deviation (n=6-9). NA: non-administration. *P<.05, **P<.01 vs placebo by Dunnett’s test. #P<.05, ##P<.01 vs placebo by Steel’s test. $P<.01 vs non-administration by Student’s t test. ++P<.01 vs non-administration by Aspin-Welch t test.

4. DISCUSSION

In this study, we investigated the effects of the novel JAK inhibitor JTE-052 on chronic dermatitis in rodent models, and compared it with existing therapeutic agents. Oral administration of JTE-052 inhibited skin inflammation in various types of dermatitis, along with suppression of inflammatory cell activation. The maximal efficacy of oral JTE-052 in skin inflammation was superior to that of ciclosporin and methotrexate in dermatitis models related to AD and psoriasis. Topical administration of JTE-052 ointment was also effective in chronic dermatitis, and its efficacy was superior to tacrolimus ointment. Furthermore, it did not cause the thinning of normal skin associated with topical corticosteroids such as difluprednate ointment.

In this study, oral administration of JTE-052 improved skin inflammation in all the tested models of chronic dermatitis. In contrast, the T cell activation inhibitor ciclosporin only reduced skin inflammation in hapten-induced chronic dermatitis in mice and had little effect on mite extract-induced or TSLP-induced AD-like dermatitis. Cutaneous T cells have been reported to contribute to skin inflammation in a hapten-induced chronic allergic dermatitis model.[22] However, although T cells contribute to mite extract-induced dermatitis,[23] mite components can also induce local inflammation directly through the activation of non-T cells.[20,21] TSLP was also reported to induce the activation of non-T cells such as dendritic cells, mast cells and innate lymphoid cells type 2 directly, but not T cells in the absence of antigens.[22] The relatively minor contribution of T cells to the pathogenesis of mite extract- and TSLP-induced dermatitis may thus explain the lack of efficacy of ciclosporin in these models. However, unlike ciclosporin, JTE-052 inhibited the activation of various types of inflammatory cells, including non-T cells and T cells, and demonstrated beneficial effects in all these dermatitis models. The different efficacies of methotrexate and JTE-052 in IL-23-induced dermatitis may have a similar explanation. Several pharmacological mechanisms of action have been proposed for methotrexate, and its anti-inflammatory effect has largely been attributed to the reduction of conventional T cell proliferation.[23] The partial efficacy of methotrexate in IL-23-induced dermatitis might thus
be explained by its limited effect on non-T cells. Overall, these findings indicate that JTE-052 exerts anti-inflammatory effects in different types of dermatitis by inhibiting various types of inflammatory cells.

In this study, serum IgE levels were increased by cyclosporin in a hapten-induced dermatitis model, as described previously. In a previous report, selective inhibition of Th1 but not Th2 by cyclosporin in vivo enhanced Th2-induced IgE production. Similarly, cyclosporin failed to inhibit IL-4 production in the ear in the current study, suggesting that partial inhibition of the Th response enhanced IgE production in this hapten-induced dermatitis model. In contrast, JTE-052 reduced IL-4 production in the ear in this model, consistent with inhibition of IL-4 in vitro, indicating that JTE-052 inhibited Th2 cells in vivo. In addition, we previously revealed that JTE-052 inhibited B-cell proliferation induced by IL-21, a cytokine indispensable for the germinal centre reaction, suggesting that its direct inhibitory effect on B cells might contribute to the decrease in serum IgE production induced by JTE-052. These findings might explain the difference between cyclosporin and JTE-052 in terms of their effects on serum IgE production. IgE is considered to play an important role in the pathogenesis of allergic diseases such as AD. Indeed, in contrast to cyclosporin that showed reduced efficacy in the late phase of the experiment in association with serum IgE elevation, the effect of JTE-052 on ear swelling lasted throughout the experiment in hapten-induced dermatitis in mice. Taken together, these findings indicate that JTE-052 may have distinct therapeutic effects from cyclosporin in these diseases via inhibition of IgE production.

Systemic immunomodulating agents such as cyclosporin and methotrexate are prevalent treatment options for the management of severe symptoms in patients with AD and psoriasis, but their usage is limited by organ toxicities including nephrotoxicity, hepatotoxicity and pulmonary fibrosis. In contrast, there have been no noticeable reports of organ toxicity associated with systemic JAK inhibitors in several clinical trials. JAK inhibitors may therefore offer a beneficial systemic medication option for chronic dermatitis, with a lower risk of side effects than conventional systemic agents. However, systemic administration of JAK inhibitors is associated with potential risks of infection and malignancies, as for other systemic agents, and topical application of JAK inhibitors may thus offer a preferable option for chronic dermatitis. Although topical corticosteroids and calcineurin inhibitors are widely used for treating chronic dermatitis without systemic toxicity, they are associated with a risk of local cutaneous side effects such as skin atrophy. Indeed, topical administration of the corticosteroid dexamethasone ointment 0.05% in the current study reduced skin thickness in normal rats, while topical treatment of JTE-052 ointment 3% had no effect on normal skin, but showed comparable efficacy to dexamethasone ointment in terms of skin inflammation in a DNBC-induced rat dermatitis model. In addition, it was recently recognised that skin barrier disruption contributes to the pathophysiology of chronic dermatitis, such as AD. As JAK inhibition by JTE-052 was revealed to improve skin barrier disruption by directly affecting epidermal keratinocytes in our previous study, topical application may be an effective dosage form for this JAK inhibitor to exert its effects on the skin barrier function. Topical application of JTE-052 may therefore be an effective novel therapy for chronic dermatitis, with a better risk profile than conventional therapies.

In conclusion, the results of this study demonstrate that JTE-052, by either oral or topical application, is a good candidate as an anti-inflammatory drug for the treatment of various types of chronic dermatitis, including AD and psoriasis, with a distinct profile from conventional therapies.

ACKNOWLEDGEMENTS

We would like to express our gratitude to Yuichi Naka (Japan Tobacco Inc.) for helpful discussion.

CONFLICTS OF INTEREST

All authors of this manuscript are employees of Japan Tobacco Inc. The authors declare that they have no other competing interests.

AUTHOR CONTRIBUTIONS

AT, YS, YY, YK (Yoshiaki Katsuda), ER, KT, KK and YK (Yukari Kimoto) contributed to data acquisition and analysis. AT, YS, WA, NK and MH contributed to the study design, data interpretation and writing of the manuscript. All authors provided critical review of the draft manuscript and approved submission of the final manuscript for publication.

ETHICAL CONSIDERATIONS

All procedures related to the use of animals in this study were reviewed and approved by the Institutional Animal Care and Use Committee of Japan Tobacco Inc. Human peripheral blood was obtained from healthy volunteers with informed consent, based on the Declaration of Helsinki.

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