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Pharmacokinetic disposition of topical phosphodiesterase-4 inhibitor E6005 in patients with atopic dermatitis

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Abstract

Background: A novel topical phosphodiesterase-4 inhibitor E6005 shows potential as effective treatment options for atopic dermatitis (AD); however, systemic exposure may cause potentially undesirable adverse reactions. In this study, we evaluated the relationship between the systemic exposure of E6005 and clinical parameters including skin condition and the incidence of AEs in patients with AD.

Methods: The association analysis used the clinical data obtained in a previously conducted clinical study with topical E6005 in adult patients with AD. To estimate associations with drug exposure, generalized estimating equation logistic regression models were used, along with clinical data and plasma concentrations of M11, major metabolite of E6005 (as an indicator for E6005 exposure).

Results: The metabolite M11 was detected in 62 of 221 plasma samples from 72 subjects. From association analysis, SCORAD-A obtained prior to E6005 treatment was identified as the clinical parameter influenced to M11 detection with statistical significance ($p = 0.003$). M11 detection was not clearly associated with the incidence of adverse events occurred.

Conclusion: Exposure to topical E6005 is associated with the eczema-associated area, however, that is not distinctly associated with its adverse drug reactions occurred after drug applications possibly due to E6005's characteristics of tissue distribution.

Introduction

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases, characterized by epidermal barrier dysfunction, eczematous skin lesions, pruritus, and immuno-dysregulation [1-3]. First-line treatments of AD include the application of emollients for barrier-disrupted skin; topical steroids or topical calcineurin inhibitors for skin inflammation; and oral antihistamines for pruritus. Second-line adjunct therapies include anti-IL-4 receptor α antibody dupilumab, systemic cyclosporine, short-term oral steroids, and ultraviolet radiation. Although many reports confirm the effects of conventional treatments, satisfaction and adherence to treatments are typically low in AD patients [4]. Therefore, development of new treatments for AD is in high demand.

Phosphodiesterase 4 (PDE4) is a major phosphodiesterase expressed in leukocytes and keratinocytes, where it hydrolyses cyclic AMP (cAMP) into AMP, which may lead to the production of pro-inflammatory cytokines [5,6]. E6005, currently in clinical development as RVT-501, is a PDE4 inhibitor with novel molecular structure, and its potent anti-inflammatory

and antipruritic action has been demonstrated in pre-clinical animal models [7,8]. In a clinical trial, topical application of 0.2% E6005 ointment for up to 12 weeks was well tolerated and effective in adult patients with AD [9]. In contrast, oral administration of PDE4 inhibitors has been associated with adverse events (AEs) such as diarrhea, weight loss, and nausea, which are ostensibly associated with their action on the central nervous system [10-12].

In this study, we characterized the relationship between plasma concentrations of the M11, major metabolite of E6005, and clinical parameters including skin condition and the incidence of AEs, using the data obtained in a previously conducted clinical study in adult patients with AD [9].

Materials and methods

The subjects participated in the present clinical research have given their informed consent and the study protocol has been approved by the institute's review board on human research.

Source of clinical data in AD

All relevant clinical data were retrieved from a clinical trial of topical E6005 in patients with AD registered as identifier NCT01461941. An appropriate amount of 0.2% E6005 ointment, or vehicle control, was applied twice a day according to the size of the lesion (0.5 g of ointment for each area covering 2% of the body surface area). The analysis set consisted of 72 subjects; 52 subjects who had been administered topical E6005 for 12 weeks through randomization phase to open-labeled phase (Group A); and 20 subjects who had been administered topical E6005 for 8 weeks in the open-labeled phase, after completion of 4-week vehicle administration in the initial randomization phase (Group B). The demographic parameters of the 72 subjects used in the analyses are shown in Table 1. The treatment compliance in this study was well controlled, and treatment rate was 94.82% and 96.13% in Groups A and B, respectively.

Blood samples were collected at 1, 4, 8, and 12 weeks in Group A and at 4 and 8 weeks in Group B after the initiation of topical E6005 administration. Plasma concentrations of E6005 and M11, formed by hydrolyzation of E6005 at the methyl ester bond, were determined using a validated method employing liquid chromatography along with tandem mass spectrometry [13], with the

lowest detectable concentration of 1.0 ng/mL for both E6005 and M11.

For determining lesional skin scores of AD, we used the standard scoring system SCORAD (SCORing Atopic Dermatitis): SCORAD-A (affected body surface area, score 0–100%) and SCORAD-B (total intensity score from six signs: erythema, edema/papulation, oozing/crust, excoriation, lichenification, and dryness, 0–18 points) [14]. The SCORAD of all patients was evaluated by trained clinical dermatologists. The incidence of AEs was summarized by System Organ Class (SOC) specified in MedDRA ver. 15.0.

Statistical analysis

The Spearman correlation coefficient was calculated to evaluate correlation between variables. The generalized estimating equation (GEE) model was used to test the association between the detection of plasma M11 concentration and each covariate as (1) the detection of M11 was a binary variable, and (2) several covariates were from the same subject at different time points [15]. The analysis was conducted using M11 detection status [yes: more than BQL (below limit of quantification: < 1.0 ng/mL), no: less than BQL] as the dependent variable, and several covariates including age, sex, body weight, time from initial administration to each assessment, time from last administration of topical E6005 to blood sampling, and clinical parameters (SCORAD-objective, SCORAD-A, SCORAD-B and its components). To account for associations between repeated measurements taken from the same subject, GEE logistic

regression analyses were used to estimate associations between the detection of M11 and each covariate. Before the GEE model analysis, the probability of detection of M11 was converted to the logit value within each subgroup (2 subgroups for sex, 4 subgroups for time from initial administration, and 10 subgroups for other categories), categorized by the order of each covariate. The logit value was given by $\ln(P / [1-P])$. In the GEE analysis, the working correlation matrix was set to exchangeable, and robust variance estimators were adopted for obtaining confidence intervals (CIs) of the estimated values. Fisher's exact test was used to compare the incidence of AEs between the detected M11 and the not-detected M11 groups. All statistical analyses were performed using SAS software (version 9.3, SAS Institute, Cary, North Carolina, USA). All quoted p-values are two-sided, with a significance level of 0.05.

Results

Plasma concentrations of E6011 and M11 after application of topical E6005

There were 221 available plasma samples collected from 72 subjects who were treated at least once with topical E6005. While all plasma concentrations of E6005 were BQL (< 1.0 ng/mL) during the study period, the metabolite M11 was slightly detected in 62 of 221 plasma samples (the maximum detected value was 13.6 ng/mL). Figure 1 showed the plots of plasma M11 concentration observed versus time from the last application of topical E6005 to blood sampling. Although PK profile was not clearly characterized since the majority of plasma M11 concentrations were BQL, plasma concentrations of M11 was most often observed approximately 2-10 hours after the last administration. No tendency of accumulation of plasma M11 level after repeated topical applications of E6005 was observed.

Correlation between plasma M11 levels and clinical parameters

The calculation of the Spearman correlation coefficient to confirm the probability of correlation between the detection of M11 in above plasma samples and several covariates suggested that there were relatively high correlations ($|r| > 0.3$) between the detection of M11 and SCORAD-A ($r = 0.42$), and between the detection of M11 and SCORAD-B ($r = 0.37$).

Table 2 shows the estimated values of association between M11 detection and each covariate.

Associations between the natural log of odds ratio for the detection of plasma M11 concentration

and SCORAD-A or SCORAD-B are also presented (Figure 2). There was a significant association between SCORAD-A and M11 detection ($p = 0.003$).

Correlation between Plasma M11 positivity and adverse events

We next examined whether the occurrence of AEs in the clinical trial was associated with the presence of plasma M11. Plasma M11 was detected in 34 out of 72 patients. As shown in Table 3, plasma M11 positivity showed no obvious association with AEs in any of the five system organ classes (“General disorders and administration site”, “Gastrointestinal disorders”, “Skin and subcutaneous tissue disorders”, “Infections” and “Others”).

Discussion

Characterizing permeability properties is critical during the development of topical drug formulations for skin diseases such as AD, in which the barrier disturbance is a cardinal feature.

In this study, the correlation of plasma concentrations of M11 and skin conditions and its influence on the safety profile of E6005 were analyzed in clinical data. We found; 1) the affected body surface area is a significantly more important factor for increasing the plasma M11 levels compared to lesional severity; and 2) the occurrence of AEs is not significantly associated with plasma M11 positivity.

E6005 itself was not detected or less than BQL in plasma samples obtained after topical E6005 application. While the plasma levels of M11 were quantified in some samples, they were low and measured only in 28% (61 out of 221) plasma samples. The profile of E6005 and M11 detections suggested 1) that systemic absorption of E6005 was negligible or very low, 2) that M11 was quickly metabolized from the absorbed E6005 and 3) that M11 also seemed to rapidly eliminate from systemic circulation. As a result, no or very low accumulation of M11 was observed during the study period where topical E6005 was repeatedly applied twice a day for up to 12 weeks.

Therefore, in the association analysis using human clinical data, we used the plasma concentration of M11 as an appropriate indicator of E6005 exposure [9]. Although the surface area of eczema showed a clear association with M11 detection in AD patients, SCORAD-B was

not clearly associated with M11 detections. Generally, SCORAD-B scores the severity intensity of the “most representative area”. The severity of skin involvement varies dramatically depending upon anatomical sites in some patients, and some anatomical parts, including the head, face and neck, are known to have different absorption rates of the topical drug compared to the body trunk. Irrespective of these characteristics, the investigators needed to show only one intensity score in the study. This may be a potential reason for the lack of association between SCORAD-B and M11 detection. We note one more thing to be considered in evaluating the obtained data.

Although transepidermal water loss (TEWL) is widely used to evaluate skin water barrier function, TEWL was not measured in the present clinical study because it was difficult to conduct TEWL measurement under specified conditions in such a multi-center trial. Some studies have suggested that TEWL correlates with percutaneous absorption of chemical compounds, while other reports did not show a clear relationship [16-20]. It is currently unknown if skin permeability of highly lipophilic E6005 correlates with TEWL. Further investigations using TEWL and clinical evaluation in pediatric population would be beneficial for understanding the more detailed characteristics of E6005 exposure via the skin in patients with AD.

The use of an oral PDE 4 inhibitor, roflumilast, as a COPD drug is limited because of systemic AEs such as diarrhea, emesis, weight loss, and headache, potentially due to its agonistic effect on the $\alpha 2$ adrenoceptor in the central nervous system [21,22]. Apremilast is currently available as

oral PDE4 inhibitor in both the United States and Europe for the treatment of psoriasis and psoriatic arthritis. Pooled safety analysis using the data from two phase 3 studies of Apremilast suggested that the most common AEs occurred through the studies were diarrhea and nausea while the report concluded that the benefit-risk profile of Apremilast is positive mainly due to its ease to use including lack of laboratory monitoring requirement, the oral route of administration and lack of cumulative, specific organ toxicity [12]. These results indicate that increased systemic exposure of PDE 4 inhibitor may cause such gastrointestinal or other unexpected AEs. In the present study, we did not obtain clear evidence to show that M11 detection was associated with the incidence of any AEs occurring in the clinical study. In addition, very low tissue penetration of topical radioactive E6005 was observed in our animal investigations using damaged skin model, probably due to the high protein binding ratios of E6005 and M11 (our unpublished data). Considering these pharmacokinetic characteristics of E6005 and M11, the occurrence of systemic AEs would be relatively low even if the topical E6005 is performed on barrier-disrupted skin in AD. This is consistent to the results from previous animal investigations in which the emetic potential of systemic E6005 administration was lesser than that of another oral PDE4 inhibitor cilomilast [8,21-23].

In conclusion from present analysis of the clinical study data of topical E6005, the exposure to topically applied E6005 in human is dependent on the skin condition, especially the area affected

by eczema, but is not directly associated with its adverse drug reactions due to its pharmacokinetic characteristics.

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Table 1. Characteristics of the analyzed 72 subjects

	Group A (E6005/E6005) (n = 52)	Group B (Vehicle/E6005) (n = 20)	Combined total (n = 72)
Age, years, mean (range)	31.4 (20–53)	31.4 (20–49)	31.4 (20–53)
Sex, n (%)			
Male	29 (55.8)	12 (60.0)	41 (56.9)
Female	23 (44.2)	8 (40.0)	31 (43.1)
Body weight, kg, mean (range)	61.8 (41.4–91.9)	60.7 (40.5–81.5)	61.5 (40.5–91.9)
SCORAD-A, mean (SD)	19.2 (8.3)	17.4 (8.7)	18.7 (8.4)
SCORAD-B, mean (SD)	7.8 (2.0)	7.0 (1.9)	7.6 (2.0)

Table 2. Factors related to the detection of plasma M11 concentration: Summary of GEE parameters.

	Estimated value (95% CI)	<i>p</i> value
SCORAD-A	0.069 (0.024 to 0.113)	0.003
SCORAD-B	0.022 (−0.176 to 0.220)	0.828
Age	−0.012 (−0.056 to 0.033)	0.600
Sex	0.028 (−1.137 to 1.194)	0.962
Body weight	−0.004 (−0.051 to 0.044)	0.884
Time from last drug application	−0.006 (−0.089 to 0.078)	0.896
Time from baseline	−0.055 (−0.160 to 0.050)	0.306

Table 3. Detection of M11 and incidence (%) of adverse events by system organ class of MedDRA

E6005-treated subjects	System Organ Class				
	General disorders and administration site conditions	Gastrointestinal disorders	Skin and subcutaneous tissue disorders ¹⁾	Infections and infestations	Others
Detected M11 (n = 34)	23.5% (8/34)	8.8% (3/34)	20.6% (7/34)	23.5% (8/34)	23.5% (8/34)
Not detected M11 (n = 38)	10.5% (4/38)	15.8% (6/38)	10.5% (4/38)	34.2% (13/38)	10.5% (4/38)
Fisher's exact test	$p = 0.206$	$p = 0.485$	$p = 0.329$	$p = 0.437$	$p = 0.206$

1) The AEs related to progression of existing disease (preferred term “Atopic dermatitis”) were excluded from the analysis.

Figure legends

Figure 1. Profile of plasma M11 concentration versus time from the last application of E6005 in each evaluation time point over 12 weeks. A number of plasma samples are 51, 64, 66 and 40 in week 1, week 4, week 8 and week 12, respectively. All concentration values below the limit of quantification are plotted as zero.

Figure 2. Scatter plot of probability of M11 detection and SCORAD-A (a) and SCORAD-B (b). Data points were indicated as mean values of logits and SCORAD-A or SCORAD-B obtained from one of ten groups consisting of approximately 20 sampling points*subjects (minimum: 11, maximum: 37) ordered by values of SCORAD-A or SCORAD-B, respectively.



