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Letter to the Editor

Poor pharmacological adherence to inhaled medicines compared with oral medicines in Japanese patients with asthma and chronic obstructive pulmonary disease

Dear Editor,

Poor pharmacological adherence (adherence) is a problem that reduces quality of life in patients with chronic diseases and leads to wastage of health care resources.^{1,2} Few comparative studies of adherence to inhaled and oral medicines have been performed in Japanese patients with asthma and chronic obstructive pulmonary disease (COPD).^{3,4} To investigate adherence levels to inhaled medicines, a multicenter, cross-sectional non-interventional trial was conducted in Japanese patients who had regular use of both inhaled and oral medicines for asthma or COPD by the Kyushu Asthma Seminar Investigator Group, which was approved by each local ethics board (UMIN No. R000015329) ([Supplementary Material: Table 1](#)).

To investigate adherence in consecutive outpatients with asthma (aged ≥ 20 and < 80 years) and COPD (aged ≥ 40 and < 80 years) who were taking at least one regular prescribed inhaled and oral medication without changes in regimens for > 6 months ([Supplementary Material: Table 2](#)), one inhaled and one oral medicine were selected as the most important among all regular prescribed medicines [mean (\pm standard deviation) was the number of different inhaled devices and oral medicines (range) = 1.1 ± 0.4 (1–3) and 4.3 ± 3.0 (1–18) available to patients with asthma; 1.5 ± 0.5 (1–3) and 5.0 ± 4.1 (1–22) in patients with COPD, respectively] by each physician without consultation with the patient ([Supplementary Material](#)). Adherence levels were examined by questionnaire and prescription refill method. The characteristics and lung function data within 6 months of patients were obtained after written consent (see [Supplementary Material](#) for definition and control levels of asthma and COPD). Poor adherence to medicines was defined on the basis of $< 80\%$ adherence to selected inhaled or oral medicines by either the questionnaire or prescription refill method.^{5,6} We statistically compared the populations of patients with poor adherence to selected inhaled and oral medicines, and calculated the odds ratios [95% confidential interval (CI)] of poor adherence to inhaled medicines in total patients (asthma and COPD), patients with asthma, and patients with COPD by using a Fisher's exact tests. By univariate and multivariate analyses, we investigated the risk factors as patient-, social-, and treatment-related factors [odds ratios (95% CI)] for poor adherence to inhaled medicines to compare patients with and without poor

adherence ([Supplementary Material: Table 4](#)).^{5,6} Differences with $p < 0.05$ were considered significant. Statistical analyses were performed using software package JMP version 9.0[®] (SAS Institute Japan Inc., Tokyo, Japan).

Of the 479 patients who provided informed consent, 372 (number of patients with Asthma-COPD overlap = 9) [248 (5) with asthma and 124 (4) with COPD] patients were part of the final analysis, and the numbers of total patients with and without poor adherence to inhaled medicines were 62 and 310, respectively ([Supplementary Material: Fig. 1 and Table 3](#)). [Figure 1](#) shows that the population of patients with poor adherence to inhaled medicines was significantly higher than that of patients with poor adherence to oral medicines in total patients (odds ratio: 8.0 [95% CI: 3.8–17.0] $p < 0.0001$), patients with asthma (10.2 [3.9–26.5] $p < 0.0001$), and patients with COPD (5.0 [1.4–18.0] $p = 0.0156$). [Table 1](#) shows that the independent risk factors for poor adherence to inhaled medicines included a poor compliance rate between scheduled appointments and clinic visits as social-related factors in total patients, once inhalation per administration as treatment-related factors in total patients and patients with asthma, and the regular usage of any nasal sprays as treatment-related factors in patients with COPD. However, the types of compounds such as inhaled corticosteroids, β_2 -agonist and muscarinic receptor antagonist and devices such as pressurized metered-dose inhaler, dry powder inhaler and soft mist inhaler were not significantly associated with any adherence levels to inhaled medicines in patients with asthma and COPD (full analysis is shown in [Supplementary Material: Table 4](#)).

To our knowledge, our study is the first study in which adherence levels between inhaled and oral medicines are compared, and the feature of poor adherence to only inhaled medicines is investigated in Japanese patients with asthma and COPD. We found that the adherence levels to selected inhaled medicines were significantly poorer than that to oral medicines in all patients, patients with asthma, and patients with COPD. However, our study demonstrated that the population of patients with good adherence to selected inhaled ($> 75\%$) and oral ($> 90\%$) medications was higher than that of patients in other countries with chronic diseases such as hypertension, diabetes, and asthma.^{1,5} The difference is still unclear; however, it may be associated with local behaviors or differences in the health care system among countries or areas. A compliance rate for the clinic visit is associated with a relationship between patients and physicians and is considered a social-related factor.^{7,8} In our study, the

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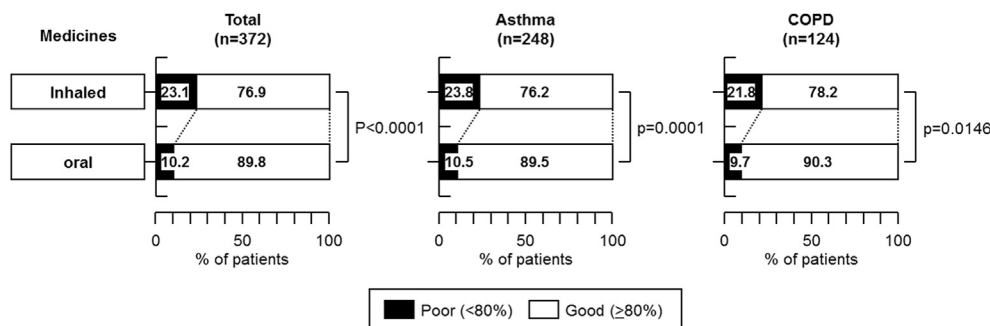


Fig. 1. Comparison of the population of patients with poor and good adherence between inhaled and oral medicines in total patients, patients with asthma, and patients with COPD by either questionnaire or prescription refill methods.

Table 1
Risk factors for patients with poor adherence to only selected inhaled medicines in patients with asthma and COPD by univariate and multivariate analysis.

Characteristics†	Univariate analysis				Multivariate analysis	
	Poor adherence to only inhaled medicines‡		Odds ratio (95% CI)	p Values	Odds ratio (95% CI)	p Values
	With n/N	Without n/N				
Total patients						
>23.0 kg/m ² of body mass index	35/62	148/310	1.4 (0.8–2.5)	0.2	–	–
Poor attention to detail in personality	14/62	34/309	2.4 (1.2–4.7)	0.0210	1.3 (0.5–3.0)	0.6
Poor compliance rate between scheduled appointments and clinic visits	8/60	7/305	6.6 (2.3–18.3)	0.0009	4.9 (1.4–18.7)	0.0144
Once inhalation per administration in selected inhaled medicines	49/62	197/310	2.2 (1.1–4.2)	0.0189	2.0 (1.0–4.0)	0.0377
Asthma						
Poor attention to detail in personality	12/41	26/180	2.9 (1.3–6.3)	0.0153	1.7 (0.6–4.4)	0.3
Poor compliance rate between scheduled appointments and clinic visits	6/39	6/202	5.9 (1.8–19.5)	0.0055	3.8 (0.9–16.7)	0.1
Once inhalation per administration in selected inhaled medicines	39/41	139/207	9.5 (2.2–40.7)	<0.0001	8.7 (2.5–54.8)	0.0001
COPD						
Regular usage of any nasal sprays in all medicines	5/21	5/103	6.1 (1.6–23.6)	0.0125	4.4 (1.0–18.6)	0.0460
>1 time of administrations per day in selected inhaled medicines	9/21	19/103	3.3 (1.2–9.0)	0.0220	2.5 (0.8–7.3)	0.1

CI, confidence interval.

† The median was used as cut-off value between high and low. The median of body mass index in total patients was 23.0 kg/m², numbers of inhalations per administration in selected inhaled medicines in total patients and patients with asthma was 1 inhalation, and time of administrations per day in selected inhaled medicines in patients with COPD was 1 time.

‡ The number of patients with positive results in each characteristics/number of total patients with and without poor adherence to only inhaled medicines was expressed as n/N. The number of patients who did not report regarding characteristics of personality was 1 (1 with asthma) and the compliance rate between scheduled appointments and clinic visits was 7 (7 with asthma).

relationships may be good, since patients with a poor compliance rate may visit a clinic without forfeits and discriminations. Previous reviews showed that complex regimens were associated with poor adherence and are considered treatment-related factors.^{7,8} We considered that poor adherence to only inhaled, not oral, medicines may be associated with the complexity of device usage. We found that fewer numbers of inhalations (once inhalation per administration) of selected inhaled medicines was an independent risk factor for poor adherence to only selected inhaled medicines rather than twice or more inhalations per administration in total patients and patients with asthma. For patients with poor adherence, respiratory physicians have a tendency to change medication regimens to make it easier to take, such as less frequency of administration, which may have led to the correlation between fewer numbers of inhalations per administration and poorer adherence observed in our study. However, we do not have data to confirm this. In patients with COPD, those with the regular usage of any nasal sprays had a significantly higher population of patients with poor adherence to only selected inhaled medicines than patients who did not use nasal spray, although the population was small (8%). It was not clear whether the regular usage of any nasal sprays was associated with poor

adherence to inhaled medicines in patients with COPD. Further studies are necessary to clarify the issue.

Our study had some limitations. First, the collected data were based on interviews and not on direct methods.^{5,9,10} Second, selection of only one medicine from inhaled and oral medication groups may have led to a selection bias in our results. Third, a patient's knowledge of taking medications at a fixed time and accuracy of inhalation technique were not investigated. We did not have observers that evaluated adherence and technique. Fourth, the efficacy and safety of inhaled and oral medicines were not compared. Fifth, the sample size of COPD patients (n = 124) may be statistically small (Supplementary Material). Sixth, we did not investigate if the factors of airway reversibility to bronchodilators were associated with poor adherence levels to inhaled medicines. Seventh, we could not address why there were fewer inhalations of inhaled medicine in patients with asthma and the regular usage of any nasal sprays in patients with COPD was an independent risk factor for poor adherence to inhaled medicines. Further studies are necessary to clarify these limitations.

In conclusion, we believe that our results will contribute to improved education and management of patients that use inhaled medicines.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alit.2016.10.008>.

Conflicts of interest

TK received grants from AstraZeneca, MSD, Novartis Pharma, and lecture fees from Novartis Pharma, GSK, Boehringer Ingelheim, Kyorin Pharmaceutical, Astellas Pharma, AstraZeneca. TKI received grants from GSK, AstraZeneca, and a lecture fee from AstraZeneca. YS received a grant from GSK, and a lecture fee from Astellas Pharma. MY received lecture fees from Boehringer Ingelheim, GSK. KT received

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