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ORIGINAL ARTICLE

Current Situation of Asthma Therapy by Allergists in Primary Medical Facilities in Japan

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ABSTRACT

Background: To reduce deaths from asthma, further use of inhaled corticosteroids (ICS) in accordance with the guidelines is required. The present study was conducted because specialists are responsible for increasing the use of guidelines, but the current state of asthma care provided by specialists in primary clinical settings has not been clarified.

Methods: In collaboration with five primary medical facilities throughout Japan, severity of asthma, contents of asthma therapy, and the implementation rate of pulmonary function testing and peak flow measurements were analyzed for 1007 outpatients ≥40 years old with stable bronchial asthma. In all patients, peak inspiratory flow (PIF) was measured during examination.

Results: Either ICS or ICS/long-acting beta 2 agonist (LABA) was used in almost all patients with at least mild persistent asthma. Although treatments adhered to the guidelines, therapeutic steps did not match asthma severity in many patients with mild intermittent asthma. Large gaps existed between facilities that measure pulmonary function and PEF in daily clinical practice and those that do not. While mean PIF value for all subjects was well maintained at 102.0 ± 29.1 L/min, some patients may not have been able to inhale efficiently in terms of PIF (5.1% of Turbuhaler® users and 5.7% of Diskhaler® users).

Conclusions: When stepping down asthma therapy, some confusion in policy may exist, leading to guideline mismatches. Differences in the implementation of pulmonary function and PEF measurements, as indicators for long-term management, need to be minimized among specialists. For maintaining effective inhalation, inspiratory flow should be periodically checked.

KEY WORDS

asthma, inhaled corticosteroid (ICS), peak expiratory flow (PEF), peak inspiratory flow (PIF), pulmonary function test

INTRODUCTION

Chronic eosinophilic inflammation of the airway is the main pathological feature of bronchial asthma. To prevent the progression of irreversible airway remodeling, inflammation needs to be controlled early.[1] At present, inhaled corticosteroids (ICSs) represent the most effective therapeutic method for controlling inflammation, and major treatment guidelines, such as those published by the Japanese Society of Allergology, recommend active usage as the main therapeutic agent in asthma therapy.[2,3] However, use of ICSs in Japan cannot be considered sufficient. According to the Asthma Insights and Reality in Japan (AIR-J) study, a telephone survey conducted by Adachi *et al.* in 2000 and then 5 years later in 2005, the usage rate of ICSs in adults increased from 12% to 18%, but this number was clearly lower than the ≥20% in Europe (Asthma Insights and Reality in Europe in 1999 [AIR-E]).[4] To improve this situation and further promote ICS usage, widespread adoption of standard therapy based on the guidelines must be promoted in primary

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Table 1 Patients characteristics

Numbers of patients	1007
Gender (Male/Female)	393/614
Mean age (year)	59.6 ± 12.6
Severity of asthma *N* (%)	
Mild intermittent	52 (5.2)
Moderate intermittent	290 (28.2)
Moderate persistent	466 (46.3)
Severe persistent	184 (18.3)
Unknown	15 (1.5)
Duration of asthma (months)	10.3 ± 12.7
<5 yr	42.5 (%)
5 - 10 yr	19.7 (%)
10-15 yr	10.5 (%)
15-20 yr	7.3 (%)
20-25 yr	3.6 (%)
25< yr	12.7 (%)
Smoking status (%)	
Present smoker	78 (7.7)
Ex-smoker	279 (27.7)
Never smoker	636 (63.2)
Unknown	14 (1.4)
Co-morbid conditions (%)	
None	40.3
Allergic rhinitis	28.8
Hypertension	18.2
Hypercholesterolemia	10.9
Diabetes mellitus	7.1
Osteoporosis	4.5
Others	each of them <3.0 (%)

clinical settings. Specialists belonging to the Japanese Society of Allergology provide care in general clinical settings, but no studies to date have investigated how these specialists provide such care and the current state of care provided by specialists remains yet to be elucidated. To promote the guidelines, it is very important: to know how specialists involved in primary care provide care according to the guidelines in routine clinical settings; to ascertain differences between actual clinical settings and the contents of guideline-based therapy; and to identify factors that prevent or limit the spread of guideline-based therapy.

Issues related to inhalation devices comprise patient-related factors preventing greater use of ICSs. Which device is selected markedly affects how efficiently an inhalant is inhaled. Two types of ICS devices are used: pressurized metered-dose inhalers (pMDIs); and dry-powder inhalers (DPIs). When physicians prescribe an ICS, the type of inhalation device is selected almost simultaneously. DPIs include fluticasone (commercial name: Flutide®, hereinafter referred to as FP) and fluticasone/salmeterol (commercial name: Advair®), and Diskus® is the main inhalation device. Fluticasone can be inhaled using Diskhaler® in a pMDI form. Turbuhaler® is a budesonide device. With DPIs, inspiratory effort is required by the patient, and low inspiratory flow makes it impossible for some patients to inhale even with effort, causing some individuals to be unable to completely inhale the prescribed dose.[5] However, how many patients maintain sufficient inspiratory flow in actual clinical settings is unclear, and the current state is unclear as few reports have examined this subject. Furthermore, bidirectional switching between DPIs and pMDIs often occurs in daily clinical practice, and investigation of to what degree patient inspiratory flow is maintained is necessary to ensure that no problems with inspiratory flow are present.

In this study, the actual condition of asthma therapy was surveyed with the cooperation of specialists belonging to the Japanese Society of Allergology, who are very familiar with the guidelines and who are active in primary clinical settings throughout Japan. In all patients, peak inspiratory flow (PIF) was measured to ascertain whether appropriate devices were being selected in terms of inhalation.

METHODS

STUDY SUBJECTS AND PERIOD

Subjects comprised consenting patients ≥40 years old with stable bronchial asthma who had been treated on an outpatient basis at one of the five medical facilities below over a 6-month period from September 2008 to February 2009. During examination, patients were confirmed to have not experienced exacerbated symptoms or asthmatic attacks for at least the last 3 months. The present survey was conducted on pure asthma patients by excluding asthma patients complicated by clear chronic obstructive pulmonary disease (COPD). The clinical significance and purpose of the study and the possible disadvantages of participation in the study were explained in detail to each patient before their enrollment in the study and a written informed consent was obtained. Personal information was carefully handled, and data were managed using initials and numbers so that individuals could not be identified. The present study was conducted based on the ethical regulations specified by the Declaration of Helsinki (as revised in Seoul 2008).

PARTICIPATING FACILITIES (FIVE SITES)

This study was performed by the cooperation of specialists in the following facilities who belong to the Japanese Society of Allergology.

Miyatake Clinic (Osaka), Oki Clinic (Tokyo), Ohmichi Respiratory Clinic (Hokkaido), Hiroshima Allergy and Respiratory Disease Clinic (Hiroshima) and Department of Internal Medicine at JA Tohno-Kousei Hospital (Gifu).

Table 2 Relationships between usage medications (%) and severity of asthma and age range

Severity	*N*	ICS	ICS/ LABA	LTRA	Theo	LABA inhalation	LABA patch	SABA inhalation	Anti-Cho	Others	Unknown
Total patients	1007	62.5	33.1	35.7†	20.6	13.4	10.4	9.8	1.5	5.4	2.2
Severity of asthma											
Mild intermittent	52	44.2	7.7	9.6	15.4	1.9	30.8†	9.6	0.0	1.9	7.7
Moderate intermittent	290	83.4	11.4	22.1†	7.9	9.3	7.2	5.5	0.0	6.6	2.8
Moderate persistent	466	57.9	40.6	36.9†	21.9	15.5	12.4	5.8	1.1	4.1	1.9
Severe persistent	184	45.1	55.4	62.5†	38.0	17.9	5.4	27.2	4.9	8.2	0.5
Age range											
<55 yr	374	57.0	39.6	36.4†	13.1	10.7	5.9	11.2	0.5	4.0	2.1
56-64 yr	269	67.3	31.6	36.8†	20.1	13.0	9.7	11.9	1.5	8.2	1.5
65-74 yr	224	62.9	29.9	36.6†	23.2	17.4	12.5	8.5	0.9	4.0	4.0
75< yr	140	67.1	23.6	30.7†	37.1	15.0	20.7	4.3	5.0	5.7	0.7

† The 2nd usage medications next to ICS or ICS/LABA in each range.

ICS, inhaled corticosteroid; LABA, long-acting beta2-adrenergic agonists; LTRA, leukotriene receptor antagonist; Theo, Theophylline; SABA, short-acting long-acting beta2-adrenergic agonists.

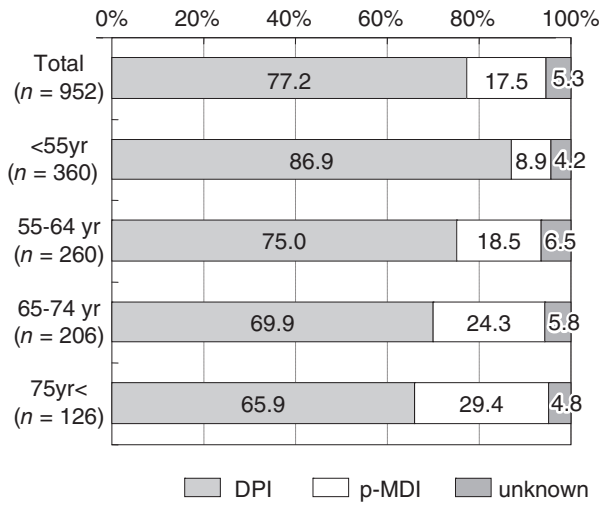

Fig. 1 Usage rates of DPIs and p-MDIs according to age range.

Table 3 Performance rates of each examinations

Faculty	Performance rate (%)			
	Number of patients	Measurement of PEF	Pulmonary function test	ACT
A	194	1.5	1.0	0.0
B	232	0.0	14.7	0.0
C	290	0.3	99.0	0.0
D	131	8.5	91.0	16.8
E	160	87.6	88.2	67.5

INVESTIGATED ITEMS

In all patients, the current severity of asthma was assessed according to the Asthma Prevention and Management Guidelines in Japan (JGL2006), based on current symptoms and administered drugs. Furthermore, disease duration, smoking status and complications were investigated. Implementation status and the results of pulmonary function tests and asthma control tests (ACTs)[6] performed in the last 6 months were examined. When peak expiratory flow (PEF) was being measured as part of routine management, these values were also analyzed. PEF was measured 3 times using a Peak Flowmeter MiniLight® (Clement Clarke International Limited, Essex, UK), and the maximum value was used for analysis. To ascertain whether patients maintained sufficient inspiratory flow and whether devices capable of efficient inspiration were selected, inspiratory flow was measured in all patients. Inspiratory flow was measured using In-check® (Clement Clarke International Limited) with an adaptor reflecting discus® resistance. Each patient was asked to perform maximum voluntary inspiration 3 times, and the largest value of the 3 measurements was used as PIF.

STATISTICAL ANALYSIS

Statistical values were expressed as mean ± standard deviation, with the level of significance set at 5%. An unpaired t test was used to compare PIF values between men and women. Multiple linear regression analysis was used for examining correlations between PIF values and other indices (Fig. 3). These statistical analyses were conducted using Excel version 4.0 software (Microsoft Co., USA).

RESULTS

During the study period, 1007 patients ≥40 years old with stable asthma consented to participate in the present study.

CURRENT STATE OF ASTHMA PATIENTS

Table 1 shows the characteristics of all patients. Among facilities that participated in the present

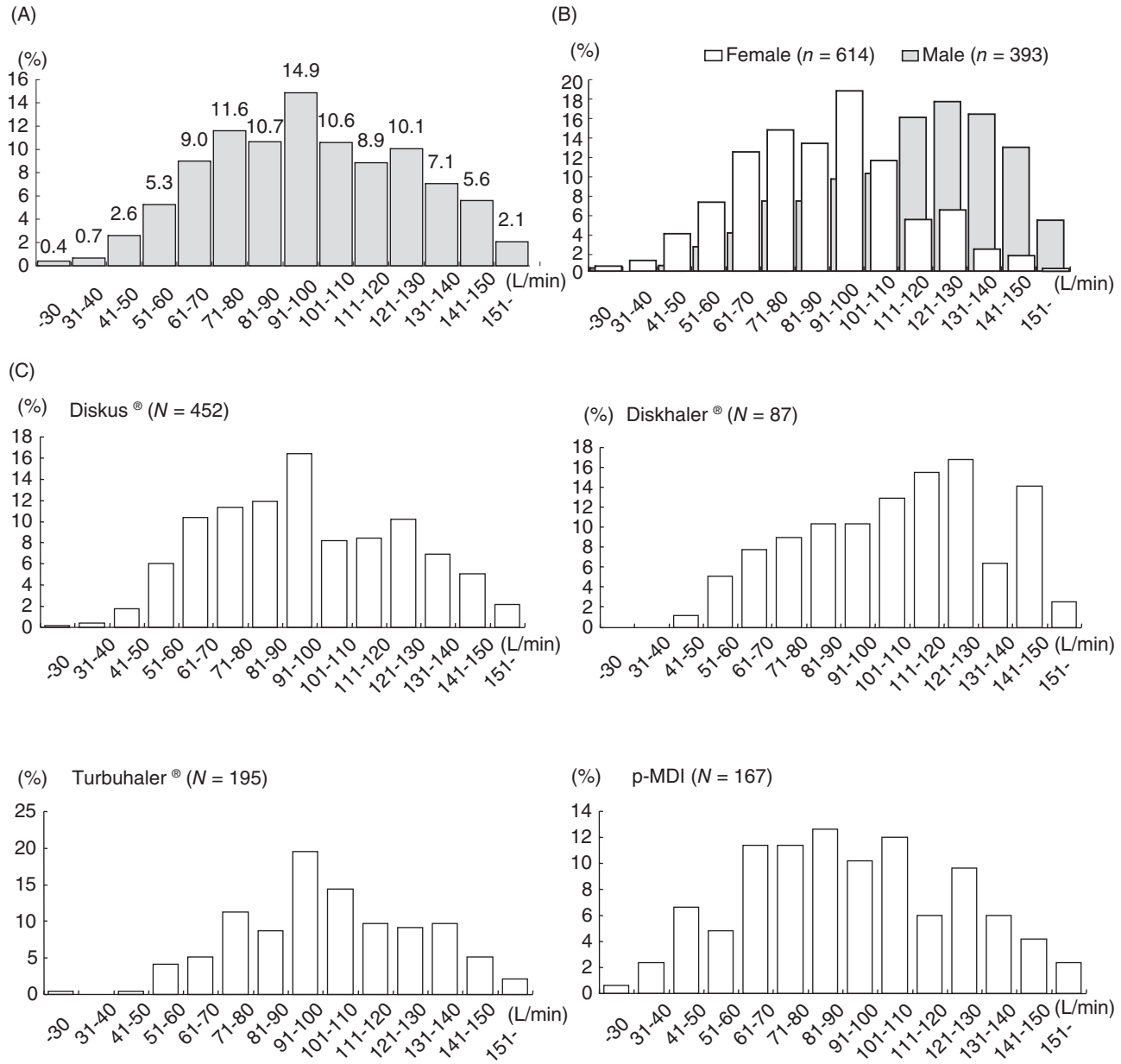

Fig. 2 Distributions of PIF values in (**A**) total patients, (**B**) male/female groups, and (**C**) each ICS usage group.

study, about 75% of patients had mild-moderate persistent asthma, and about 20% had severe asthma, whereas only about 5% had mild intermittent asthma. Of the total, 40.3% did not have complications and had only asthma. Since patients complicated by COPD were excluded from the present study, the most common complication other than COPD was allergic rhinitis (28.8%), followed by hypertension, hyperlipidemia and diabetes, in that order, and showing that complication with lifestyle diseases was common. Among the present total patient population, mean duration of asthma was 10.3 ± 12.7 years.

Table 2 shows the usage rate of drugs, including ICSs. In almost all patients with at least mild persistent asthma, either ICS or ICS + LABA was administered. Mismatches were found between the severity of asthma before starting the JGL2006 guideline treatment and currently administered drugs in the step of mild intermittent asthma. ICSs were administered to 44.2% of patients with mild intermittent asthma. On the other hand, four patients with mild intermittent asthma (7.7%) were using ICS + LABA, which was not in accordance with the JGL2006. Among the 30.8% of patients with mild intermittent asthma who used LABA patch, nine patients were using only LABA patch. Another four patients with mild intermittent asthma used more than two drugs among ICS, LTRA, theophylline and LABA patch. Irrespective of sever-

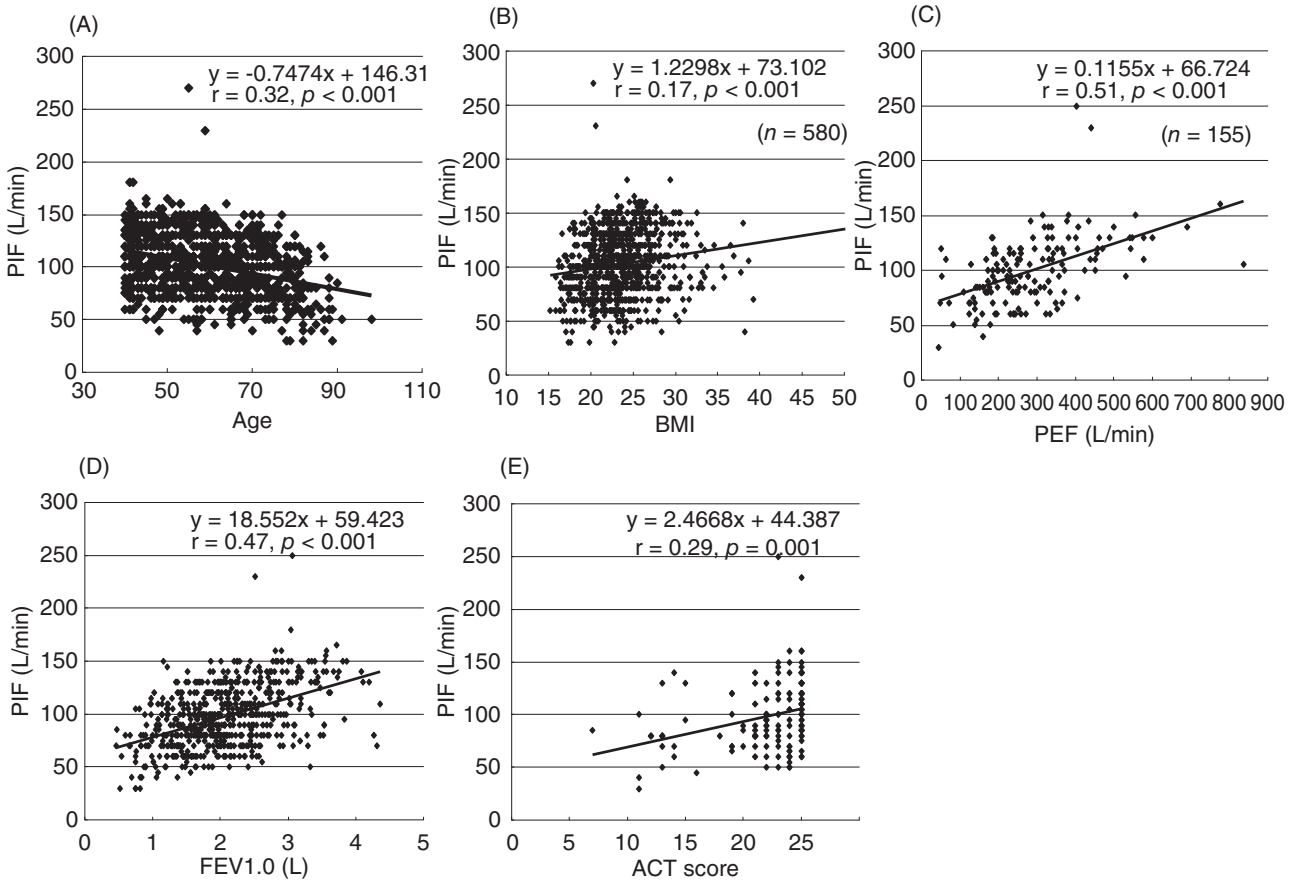

Fig. 3 Correlations between PIF values and: **A**) age; **B**) body mass index (BMI); **C**) PEF values; **D**) FEV1.0 values; and **E**) ACT scores.

ity, leukotriene receptor antagonist (LTRA) was preferentially coadministered with either ICS or ICS + LABA. The usage rate of currently prescribed drugs was analyzed in relation to age, and irrespective of age, either ICS or ICS + LABA was prescribed to most patients, with LTRA frequently used as a concurrent drug (Table 2). Figure 1 shows the usage rate of each ICS type, i.e. DPI or pMDI, in all age groups. Older patients tended to show greater use of pMDIs, suggesting that primary physicians tend to select a device by taking into account age-related decreases in inspiratory flow. No notable tendency existed in the use of DPI or pMDI in relation to severity of asthma (no data shown).

IMPLEMENTATION RATE OF PULMONARY FUNCTION TEST, PEAK FLOW MEASUREMENT AND ACT

Table 3 shows the implementation rate of each test over the 6-month period at each facility. Marked differences were identified in the implementation rate of tests in daily clinical practice among the facilities. In particular, facilities could be divided into both extremes of those that almost routinely conducted pulmonary function tests, and others that rarely conducted pulmonary function tests. Except for one facility, PEF was not routinely measured. This reflects the current situation in which routine testing is difficult in busy primary clinical settings.

PIF

Among the total patient population, mean PIF was 102.0 ± 29.1 L/min. The results of PIF values according to the severity of asthma (Step of asthma) were 89.5 +/- 27.8 (L/min) (Step I, n = 52), 105.04 +/- 28.9 (L/min) (Step II, n = 290), 102.1 +/- 28.8 (L/min) (Step II, n = 464), and 99.4 +/- 30.1 (L/min) (Step IV, n = 183). There was no statistical significance among the above four groups. Figure 2A shows the distribution among patients. PIF was ≤30 L/min for only 4 patients (0.4%), and these 4 patients had severe persistent asthma. Figure 2B shows the distribution of PIF values among male and female patients. Mean PIF was significantly higher for male patients (118.9 ± 28.6 L/min) than for female patients (91.1 ± 23.8 L/min; p < 0.001). When comparing PIF in relation to ICS agent forms, mean PIF was 103.7 ± 28.0 L/min for DPI patients and 96.4 ± 31.4 L/min for pMDI patients (p = 0.006), showing a tendency toward pMDI usage in patients with low PIF values. Figure 2C

shows the distribution of PIF values for each ICS.

CORRELATION BETWEEN PIF AND EACH INDICATOR

Figure 3A-E shows the correlation of PIF values to age, body mass index (BMI), PEF, forced expiratory volume during 1 second (FEV1.0) and ACT scores. PIF exhibited a significant negative correlation to age and a significant positive correlation to PEF, FEV1.0 and ACT score.

DISCUSSION

In the present study, with the cooperation of five allergists who were very familiar with the guidelines and were involved in primary care throughout Japan, we investigated the current state of primary asthma therapy provided by specialists. About 75% of patients examined had mild to moderate persistent asthma, and about 20% had severe asthma. This shows the current state of patients visiting allergists in primary clinical settings. The usage rate of ICS or ICS/LABA was very high, and ICSs were actively prescribed in accordance with the guidelines. The present study examined care provided by only five specialists, not all specialists in the Society, but we believe that the present results are unlikely to differ widely from the therapeutic content of the current primary care provided by other specialists in Japanese primary clinical settings. This study clarified three characteristics.

First, particularly among patients with mild intermittent asthma, therapeutic steps as viewed from currently prescribed drugs did not match the severity of asthma as indicated by primary physicians in many cases. In the present patient group, patients with stable asthma who had no symptoms within routine long-term management were selected, and steps (disease stages) ascertained based on asthma symptoms were "step 1" in most patients (mild intermittent asthma), with a small ratio of step-2 patients (mild persistent asthma). According to JGL2006, a single agent (low-dose ICS, LTRA or theophylline) should be used in patients with mild intermittent asthma. For patients in the present study with mild intermittent asthma, the sum of ICS, LTRA and theophylline usage rates was about 70% (Table 2). However, four patients with mild intermittent asthma (7.7%) used ICS/LABA. And another nine patients were using only LABA patch. Four patients also used more than two drugs among ICS, LTRA, theophylline and LABA patch. Those patients were not treated in accordance with the JGL2006. In the present study, the usage rate of LABA patch was particularly high in patients with mild intermittent asthma, as LABA patches are easy to use. Furthermore, according to the Salmeterol Multi-Center Asthma Research Trial conducted in the United States, the incidence of adverse reactions in patients on LABA monotherapy was significantly high among African Americans,[7] and although specialists avoid LABA monotherapy, since there have not been reports of severe reactions with LABA patch, the risk for LABA monotherapy in asthma may not be well recognized. However, we believe that there are bigger reasons why standard therapy is not being followed. After the diagnosis of asthma, guideline-based therapy is performed for a certain period of time, and almost all patients eventually improve to a stable asymptomatic state. It has been reported in recent years that, by performing guideline-based therapy, therapy compliance improves to significantly reduce symptoms, subsequently significantly reducing ICS use and the associated medical costs.[8] Although the guidelines mention stepping down after achieving an asymptomatic stable state for $\geq$3 months, some degree of confusion remains about the step down in actual clinical settings due to the fear of attack and exacerbation. When a state is achieved in which step down is possible, some physicians reduce or discontinue ICS in about 3 months in accordance with the guidelines, while others continue to administer ICS for a longer period of time. The underlying reason for this is that the guidelines do not clearly state which clinical indicators should be used for a step down or the rationales for indicators and timing. As a result, particularly in mild intermittent patients, confusion in the primary clinical setting causes a mismatch between severity and actual therapy.

Second, some facilities routinely measure pulmonary function and peak flow in daily clinical practice, but some facilities did not measure these at all during the 6 months, and marked differences existed in the rate of implementation (Table 3). The convenience and usefulness of ACT for controlling asthma has been recognized, but marked differences exist in the implementation rate among facilities, and this test cannot be said to be sufficiently conducted in daily clinical practice. When therapy is initiated based on the guidelines, pulmonary function findings, PEF values and ACT scores are also used as control indicators as symptoms improve. Most patients subsequently reach an asymptomatic stable state. In this stable state, PEF values and pulmonary function parameters mainly reflecting the central airway, such as FEV1.0, reach a plateau. As a result, in very busy primary clinical settings, the necessity of continuous measurements is emphasized less, lowering the rate of implementation.

Third, in the present study, PIF was measured in all subjects. Even among patients examined by specialists, appropriate devices were not being selected based on PIF in some patients. As specialists, measuring PIF in daily clinical practice and selecting more appropriate devices is even more important. For Diskus users, if PIF is within a range of 30-90 L/min, the volume of drug inhalation can be maintained in a stable manner mostly irrespective of PIF values.[9] In

the present study, the number of patients with PIF <30 L/min in whom DPI inhalation was considered difficult was unexpectedly low (n = 4, 0.4%), suggesting that Diskus® can be used in almost all patients. Also, bidirectional switching between DPIs and pMDIs often occurs in daily clinical practice, but Diskus® users do not need to make a switch to a pMDI based solely on inspiratory flow. In particular, pMDIs tended to be preferred over DPIs in older patients (Fig. 1), but from a perspective of inspiratory flow, Diskus® users do not need to make a switch to a pMDI. With Turbuhaler®, drug inhalation is considered possible with PIF ≥30 L/min,[10] but various studies have reported that PIF ≥60 L/min is required to efficiently deliver budesonide particles into the lung.[11,12] The present study used the Diskus adaptor, and since device resistance is greater for Turbuhaler® than for Diskus®, some Turbuhaler® users with PIF <60 L/min (5.1%) may not be inhaling efficiently (Fig. 2C). In the same manner, for Diskhaler® users with PIF <60 L/min (5.7%), the amount of residual powder following inhalation is high,[5] demonstrating a lack of effective inhalation. With both Diskus® and Turbuhaler®, once PIF values exceed 90 L/min, deposition in the throat increases, hindering efficient inhalation.[13] However, inspiratory flow in the present study was measured to ensure that minimum inspiratory flow was maintained. PIF was subsequently measured with maximum voluntary inspiration. Therefore, in patients with PIF >90 L/min, inhalation needs to be practiced using a device such as InCheck® to achieve the most suitable inspiratory flow for each device. In the present study, PIF values exhibited a significant positive correlation to PEF and FEV1.0 (Fig. 3C, D) and a weak positive correlation to ACT score (Fig. 3E), confirming their usefulness as indicators of asthma control. According to Banno *et al.*, PIF correlates significantly to PEF, and performing therapy based on PIF values reportedly resulted in more appropriate patient control and better pulmonary function.[14] In this study, when we made the study protocols, we made a decision to collect outpatients with asthma aged ≥40 y/o. The major reason why we collected the data from asthmatics aged ≥40 years old in this study was the comparison with the data of patients with COPD. We performed a separate survey study concerning the PIF values of patients with COPD, at the same time as this survey study. In that study, the average of the PIF values was 97.5 +/- 29.6 (L/min) (n = 175). However, the averages of PIF values were shown to decrease according to the stage of COPD; 104 +/- 27.0 (L/min) (Stage I, n = 40), 108.5 +/- 28.0 (L/min) (Stage II, n = 58), 91.0 +/- 25.9 (L/min) (Stage III, n = 40), and 70.9 +/- 23.8 (L/min) (Stage IV, n = 22, p < 0.001 compared with those of Stage I). On the other hand, the averages of PIF values were significantly unchanged according to the severity of asthma (Step of asthma) in this study. That is a major point of difference in PIF values between the results of patients with asthma and those of COPD.

In November 2009, the 2009 Asthma Prevention and Management Guidelines in Japan (JGL2009) were released.[15] One major improvement in these guidelines was that changing therapeutic steps in response to control is outlined more clearly. Severity of asthma and current therapeutic steps have conventionally been used interchangeably, but are clearly differentiated using expressions indicating severity, rather than numbers 1-4. Furthermore, starting with mild intermittent asthma, active use of ICSs as the first choice of drug is recommended, and dose of ICS in each step is changed from "consider use", "low dose", "moderate dose" and "high dose" to "low dose", "low to moderate dose", "moderate to high dose" and "high dose" to give the range of dosages within steps to facilitate dose adjustment. As also shown in the present study, the new guidelines help specialists who sufficiently prescribe ICSs to form clearer thought processes, and mismatches between severity and ICS usage are minimized, thus making the guidelines more useable for clinicians in situ. Compared to the GINA (Global Initiative for Asthma), the new guidelines set clearer goals for achieving more complete asymptomatic control, matching the lofty goal of specialists who do not want anyone in Japan dying of asthma.

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