—Regular Articles—

Cost-Effectiveness of Including Salmeterol in Asthma Therapy in a Primary Care Setting in Japan

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To discuss and estimate the clinical and economic benefits obtained during combination therapy with inhaled corticosteroids (ICS) plus salmeterol (SLM) for Japanese patients with asthma on the basis of the Global Initiative for Asthma (GINA) Guidelines. Fifty-four cases aged>16 years with either moderate persistent asthma (step 3) or severe persistent asthma (step 4) were assessed in a retrospective survey. Participants must have been a patient at the author's clinic continuously from June 2001 and been users of SLM for more than one year. Signed informed consent was obtained. Both clinical and economic components of SLM use in asthma therapy over the past two years were evaluated. Cost analyses revealed that SLM use significantly reduced medical costs of leukotriene receptor antagonist and short-acting inhaled β_2-agonists. Moreover, clinical outcomes (e.g. symptom-free day) were significantly improved after initiation of SLM. Sensitivity analyses confirmed that use of SLM is cost-effective. Combination therapy with inhaled corticosteroids and SLM on the basis of GINA guidelines appears to be efficacious and cost effective for the treatment of moderate or severe persistent asthma in Japanese patients.

Key words——salmeterol; cost-effectiveness; asthma; pharmacoeconomics

INTRODUCTION

Salmeterol xinafonate (SLM, Serevent®) is a new inhaled phenylethanolamine β_2 receptor-stimulating bronchodilator (β_2 stimulant) developed by Glaxo R & D, UK (currently GlaxoSmithKline R & D). In comparison to existing β_2 stimulants, SLM has a greater affinity for β_2 receptors and long-term sustained action, though the onset of its action is slow. Therefore, SLM is used regularly to prevent the onset of asthma attacks whereas existing β_2 stimulants are used in single doses to relieve ongoing attacks. Internationally, Seretide® (outside US)/Advair® (US) (ST), which is a combination of fluticasone propionate (FP, Flutide®), an inhaled corticosteroid (ICS), and SLM, has been marketed as contributing to improvement in health-related quality of life (HRQoL).[1)]

Bronchial asthma is a chronic inflammatory disease accompanied by obstructed airways. Therefore, administration of oral steroids and anti-allergic agents to suppress inflammation of the airway, and administration of xanthine derivatives and β_2 stimulants to relieve occlusion of the airway, are common practice in asthma management. In Japan, combinations of these drugs are frequently used in primary care depending on the patients' condition.

SLM was introduced more than 10 years ago internationally, but was not marketed until June 2002 in Japan, where it is now commonly used in asthma therapy. There has been some concern that administration of an inhaled drug might be a burden on patients who are already taking a number of oral drugs (anti-allergic agents, xanthine derivatives, etc.) and ICS. However, as we reported separately,[2)] a patient questionnaire survey showed that an additional inhaled drug could be administered without adding an emotional burden provided that guidance for the use of the therapy was given. It has also been shown that a statistically significant loss of labor productivity in Japanese patients may be avoided with therapy, both in the paid and unpaid workforce.[3)]

Guidelines for treatment and management of asthma from the NHLBI (National Heart, Lung, and Blood Institute)/WHO (World Health Organization) known as GINA (Global Initiative for Asthma)[4)] recommend combination therapy with ICS and long-acting β_2-agonists (LABA) for the treat-

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ment of moderate (step 3) to severe (step 4) chronic asthma. In Japan, the positioning of LABA has been based on the revised version of the guidelines relating to the treatment and management of asthma issued by the Japanese Society of Allergology in 2003. It adds that combination therapy with ICS and LABA is ''useful for poorly controlled asthma'' according to the assessment of EBM (evidence-based medicine) for medical techniques given by the UK medical association.[5]

Furthermore, we started to doubt the necessity of multiple oral therapies in Japan as reports stating that the combination of ICS and LABA alone could improve clinical,[6,7] humanistic (patient-reported outcomes such as HRQoL)[8] and economic[9] outcomes in comparison to a combination of ICS and oral drugs as appeared sporadically in other countries. Thus, we considered it necessary to examine the clinical and economic effects of the combination of ICS and LABA (SLM in particular) given in accordance to the GINA Guidelines in Japan. To quantify the benefits of asthma treatment in compliance with the GINA Guidelines, we retrospectively examined medical records kept at Miyagawa Clinic, Japan.

METHODS

Study Design This is a longitudinal retrospective study designed to comparatively examine the impact of SLM by assessing outcomes during the years before and after its introduction.

A cost-effectiveness analysis (CEA) was performed to examine the clinical and economic impact from the payer's perspective. The duration of analysis was set at one year in order to compare pre- and post-SLM outcomes. Discounting,[10] used widely in economic analyses, was not employed because the consumer price index[11] from 2001 to 2003 remained at almost the same level of -0.3 to -0.9% as compared to the previous year.

Subjects and Data Collection Using a 2-step sampling method, study participants were selected from a population of 1080 patients who had consulted our hospital in 2002. To be eligible for inclusion, patients were required to be ≥ 16 years of age (no upper limit of age), with a diagnosis of step 3 to 4 bronchial asthma and be receiving combination therapy consisting of ICS plus leukotriene receptor antagonist (LTRA), inhaled short-acting β_2 stimulants (SABA), and/or sustained theophylline (SRT), etc. In addition, patients were required to have no serious comorbidities and must have been receiving stable doses of medication for asthma, other than ICS, prior to receiving SLM. Approximately 270 patients met the criteria for inclusion. Twenty-four months of patient data (June 2001 to May 2003) relating to demographics, clinical findings, medical fee points, daily symptoms, and number of unscheduled visits requiring a drip infusion of either corticosteroids or aminophylline, were collected retrospectively from medical records and asthma diaries of subjects who were selected at random and agreed to participate in the study. Final data were extracted retrospectively from medical records and asthma diaries, and entered into the database using Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA).

Clinical Outcomes Clinical outcomes were defined as symptom-free day (SFD), symptom-free night (SFN), and daily peak expiratory flow (PEF) rate, as a measure of pulmonary function. SFD was the primary end point because absence of asthma symptoms for 24 hours was clinically relevant to the patient's HRQoL and productivity. The definitions of SFD and SFN were as follows:

SFD: The number of days during which asthma symptoms were completely absent for 24 hours in a patient's asthma diary.

SFN: The number of days during which asthma symptoms were completely absent during the night in a patient's asthma diary.

Costs and Related Items Costs were investigated based on detailed statements of medical costs kept at Miyagawa Clinic. Medical costs were calculated by multiplying 10 yen by one fee point (e.g. a 1,000-fee point is equal to 10000 yen). Costs were also reported in US dollars, by using the mean annual central conversion rate for Yen to US dollars ($US1=111.27 yen). This was based on the average rate issued by the Bank of Japan between June 2003 and July 2004.

Cost items: Costs included those related to medical costs (consultants, additional overtime, outpatient management), guidance costs (fees for intractable diseases guidance, drug information, asthma treatment control, continuous management), prescriptions (intractable disease prescription, basic prescription technical fee, prescription fee, oral single-dose drugs for outpatients, topical prescriptions), injections, drugs (SRT, oral β_2 stimulants, β_2 stimulant patch, SABA, LTRA [use of montelukast], oral

steroids, ICS, SLM, injection/drip infusion), and costs for laboratory tests, image diagnosis, and treatment.

Fee-related Items: Number of physician visits, number of unscheduled visits.

Ethical Considerations Prior to starting the investigation, the contents of the survey were explained to, and a written consent was obtained from, all subjects in compliance with the ethical guidance in epidemiological studies published by the Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare on July 16, 2002, and its draft (February 2002).[12]

Summary Analysis The backgrounds of the subjects at baseline were examined as demographic characteristics. The statistical values of the outcome, costs and cost-related items before and after the introduction of SLM were compared using the non-parametric Wilcoxon signed-ranks test or parametric paired *t*-test. Before performing the paired *t*-test, equality of variation was examined by the F test to judge whether the data were distributed equally before and after the introduction of SLM. The risk difference (RD) of the mean values before and after the introduction was calculated and 95% confidence intervals (CI) were determined for each item of the clinical outcomes, cost items and cost-related items. PEF values before and after the introduction of SLM were compared using Wilcoxon signed-ranks test and trends in PEF values during 24-month observation by non-parametric Kruskal-Wallis test.

Data were considered statistically significant at the 5% level. Analysis software included SPSS (Base 11.0J, SPSS Japan Inc., Tokyo), Microsoft Excel 2000 and Microsoft Visual Basic 2000.

Sensitivity Analysis The cost-effectiveness of SLM was examined by changing the respective factors including SFD, SFN and total cost between the upper and lower limits of their 95% CIs to confirm robustness of the cost-effectiveness in the base cases evaluated by the indices of point estimation as the mean.

Further, the cost-effectiveness plane (CEP) was drawn with SFD along the horizontal axis and cost along the vertical axis, and 90% and 95% CIs were also plotted by the two-dimensional normal distribution. Then, the correlation between the SFD and the cost (Pearson's correlation coefficient) was estimated.

The stochastic sensitivity analysis using a Monte Carlo Simulation, which is a parametric method, on 10000-time trials was performed in order to describe normal distributions of cost and effectiveness.

Subgroup Analysis As we reported separately,[3] it was possible to evaluate productivity loss for paid employees out of eligible subjects for analysis by the Human capital approach and, thus, CEA and cost-benefit analysis (CBA) were performed for the subgroup of employed patients from the societal perspective. The mean income of employees was calculated with respect to gender and appointment based on the wages of employees and part-timers in the three major industries (manufacturing, construction and mining) published in the labor statistics (2002) of the Ministry of Health, Labour and Welfare.[13] Loss of productivity was calculated assuming that severe, moderate and mild attacks, stridor and absence of attacks in the asthma diary corresponded to 100%, 75%, 50%, 25% and 0% loss of productivity, respectively.

RESULTS

Of approximately 270 patients who met the criteria for inclusion, 107 patients consulted the hospital during the one-month selection period, and fifty-four subjects (acceptance rate: approximately 50.5%) has finally agreed to participate in the survey.

Patient Characteristics Fifty-four subjects were included in the final analysis; 63% were female and 37% were male, the mean age was 60.2 years, 78% of patients had moderate persistent asthma (step 3), 11% had severe persistent asthma (step 4), 89% of patients had comorbidities such as allergic rhinitis and 61% of patients were in paid employment (Table 1).

Pulmonary Function (Morning PEF) Daily pulmonary function values could be derived from asthma diaries in 35 patients. Compared with before the introduction of SLM, a statistically significant improvement was seen in morning PEF ($p<0.001$, mean difference: 30.9 ml/min, 95%CI: 23.4—38.2; Fig. 1). A statistically significant change ($p<0.001$) was also seen in trends in PEF values during the 24-month assessment period, (Fig. 1).

Base Case For the base case comparison evaluated at the point estimate, a statistically significant improvement was seen in clinical outcomes such as SFDs and SFNs (per year), whereas no statistical difference was noted in the mean cost. However, a

Table 1. Demographic Information on Fifty Four Analyzable Patients at Baseline

	Item	No of case (%)		Item	No of case (%)
	Total No.	54	Type 1	Acute	0(0)
Sex	Female	34(63)		Chronic	54(100)
	Male	20(37)	Type 2	Atopic	1(2)
Age	≤29	2(4)		Infection	15(28)
	30-39	2(4)		Mixed	38(70)
	40-49	4(7)	Type 3	Seasonal	0(0)
	50-59	16(30)		Perennial	54(100)
	60+	30(55)		Mixed	0(0)
	Mean (SD)	60.2±13.6	Dosage of SLM	50 μg	6(11)
Severity*	Step 1	0(0)		100 μg	39(72)
	Step 2	6(11)		50 to 100 μg	9(17)
	Step 3	42(78)			
	Step 4	6(11)			
Job	Paid	33(61.1)		Comorbidity	48(89)
	Unpaid	21(38.9)		No-comorbidity	6(11)

SLM: salmeterol. SD: standard deviation *: Severity was diagnosed based on the GINA guideline.

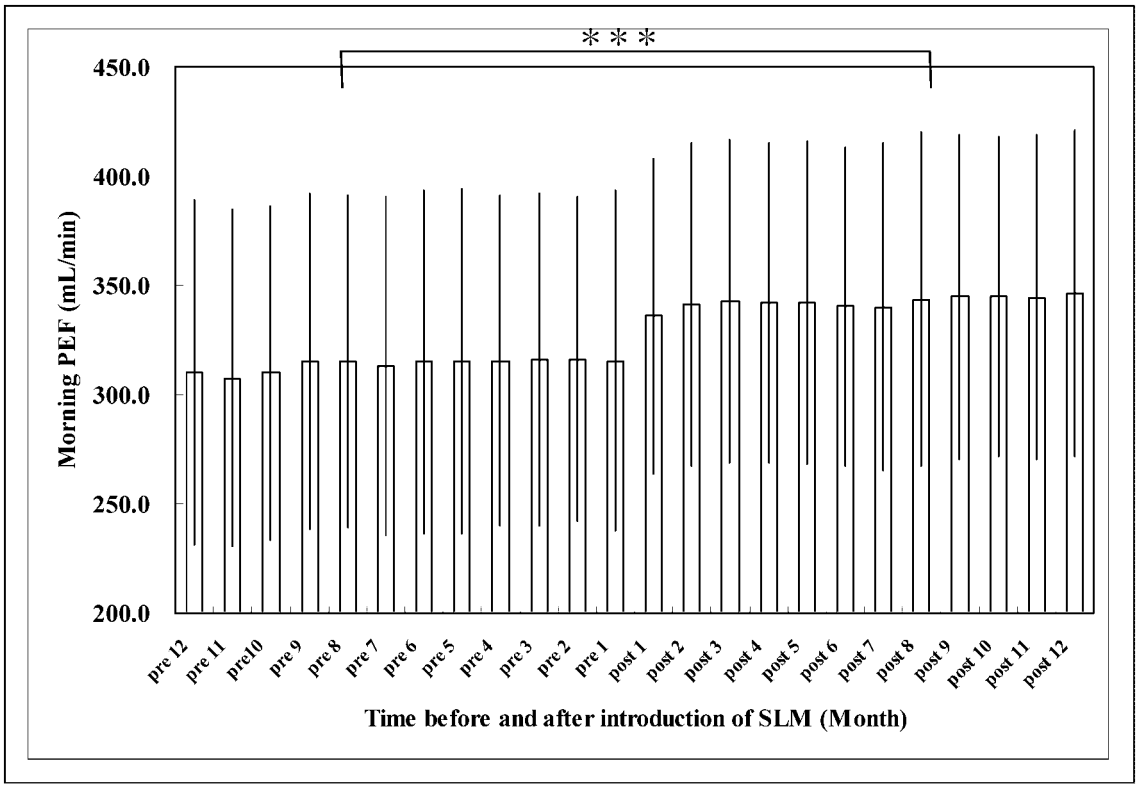

Fig. 1. Mean Morning Peak Expiratory Flow (PEF) Rate before and after the Introduction of Salmeterol (n=35)
Vertical bars represent the standard deviation. ***$p<0.001$ for comparison of PEF values before and after the introduction of salmeterol (Wilcoxon signed-ranks test). $p<0.001$ for trend in PEF values across the 24-month study period (Kruskal-Wallis test).

cost-saving of approximately 2700 yen ($US24) was obtained, as shown at Table 2. A further cost-effectiveness analysis revealed that both the cost per SFD and cost per SFN were dominant after the introduction of SLM, as shown at Table 3.

Sensitivity Analysis When a sensitivity analysis

Table 2. Cost-effectiveness Analysis on the Base Case from the Payer's Perspective ($n=54$)

Item	Before	After	Difference	95%CI	p^*
Effectiveness					
SFDs	65.7	201.5	135.8	103.9 to 167.8	<0.001
SFNs	241.4	302.0	60.6	18.0 to 103.1	<0.001
Direct cost	¥203,258 ($US1,829.14[a])	¥200,530 ($US1,802.19)	−¥2,728 (−$US24.52)	−¥20,189.1 (−$US181.44) to ¥14,733.9 ($US132.41)	NS 0.86
ICER					
Cost/SFD	—	—	Dominant[b]	N/A	N/A
Cost/SFN	—	—	Dominant	N/A	N/A

* Wilcoxon signed-ranks test. SFD: Symptom-free day, SFN: Symptom-free night, ICER: incremental cost-effectiveness ratio, CI: Confidence interval, NS: not significant, N/A: not available.
a) Currency exchange for US dollar ($US1=¥111.27, central rate average for 2003/04 published by the Bank of Japan). *b*) Dominant indicates that a new regimen is both clinically and economically superior to an alternative (e.g. pre-introduction).

Table 3. Two-way Sensitivity Analysis from the Payer's Perspective ($n=54$)

Item	Confidence interval	
	Best case	Worst case
ICER		
SFD	Dominant[a]	¥1,701.4 ($US15.29[b])
SDN	Dominant	¥9,822.6 ($US88.28)

ICER: incremental cost effectiveness ratio (incrmntl cost per incrmntl effectiveness). *a*) Dominant indicates that a new regimen is both clinically and economically superior to an alternative (e.g. pre-introduction). *b*) Currency exchange for US dollar ($US1=¥111.27, central rate average for 2003/04 published by the Bank of Japan).

Table 4. Stochastic Sensitivity Analysis Using a Monte Carlo Simulation on 10000-time Trials.

		Cost	Effectiveness
	Mean	−3,245.6 yen (US$−29.7[a])	11.3 days
95%CI	Lower limit	−4,507.9 yen (US$−40.5)	11.1 days
	Upper limit	−2,001.3 yen (US$−18.0)	11.5 days

CI: confidence interval, *a*) Currency exchange for US dollar ($US1=¥111.27, central rate average for 2003/04 published by the Bank of Japan).

was performed to examine outcomes in the base case by varying the clinical outcomes of SFD and SFN and the cost between the upper limit and lower limit of the respective 95% CIs, it was shown that all the clinical outcomes were dominant after the introduction of SLM in the best case scenario. In the worst case scenario, the incremental cost-effectiveness ratio (ICER) for the respective clinical outcomes was calculated to be approximately 1700 yen ($US15)/day with respect to SFD and 9800 yen ($US88)/day with respect to SFN.

When the results were plotted on the CEP and drawing of 90% and 95% CIs in the two-dimensional normal distribution was attempted, it was found that some of the cases were inferior as shown in Fig. 2. The Pearson's correlation coefficient (r) was 0.180 ($p=0.192$) and no statistically significant correlation was noted.

When a Monte Carlo Simulation on 10000-time trials was performed for the stochastic analysis, whereas a mean cost was saved of approximately 3200 yen (US$29.2, 95%CI: 4500 to 2000 saved), a mean SFD was increment of approximately 11.3 days (CI: 11.1 to 11.5) after use of SLM, as shown at Table 4.

Subgroup Analysis Subgroup analysis was performed for clinical outcomes, cost and evaded productivity loss for 33 paid employees with asthma. As shown at Table 5, the clinical outcomes of SFD and productivity loss were improved significantly while a significant reduction of about 70000 yen ($US629) was noted in the total cost (the sum of the cost and the evaded productivity loss). As the results were dominant after the introduction of SLM, the evaded productivity loss per SFD or ICER, which is the ratio of the total cost, was not calculated separately. However, although not statistically significant, an incremental cost of about 7000 yen ($US63) was evident, and the ICER with SFD as the effect was calculated at 60 yen ($US0.5)/day. Furthermore, CBA was performed to calculate the net benefit from the evaded productivity loss and it was found that about

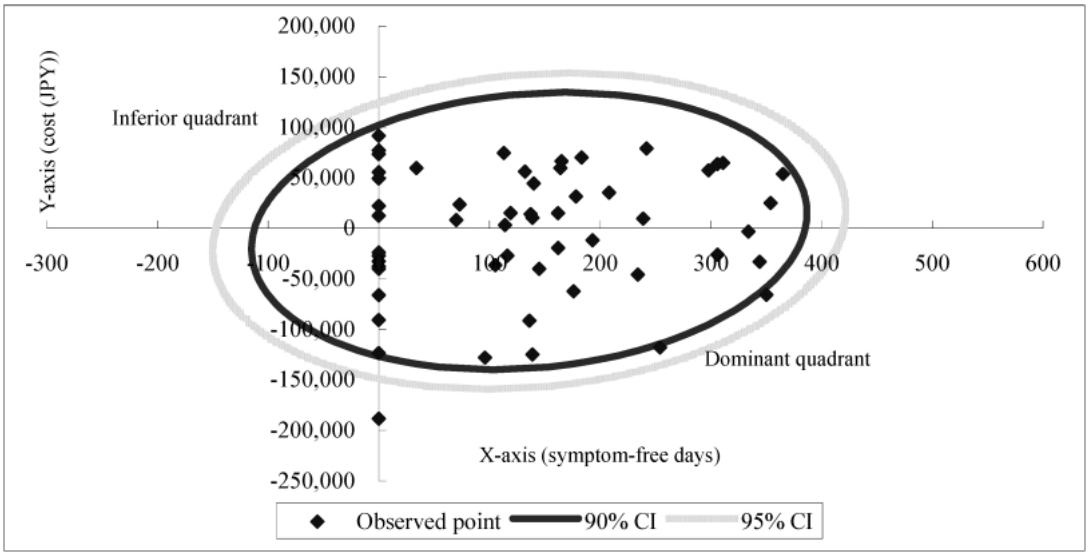

Fig. 2. Cost-effectiveness Plane on Cost (Yen, Y-axis) per Symptom-free Day (Days, X-axis) (n=54)
r=0.180, p=0.192, CI: confidence interval.

Table 5. Cost-effectiveness/Cost-benefit Analyses for Subgroup (Paid Subjects only, n=33) from the Societal Perspective

Item	Before	After	Difference	95%CI	p*
Effectiveness					
SFDs	75.1	195.9	120.7	83.2 to 158.2	<0.001
Cost					
Direct	¥195,518 ($US1,757.15)	¥202,831 ($US1,822.87)	¥7,313 ($US65.72)	−¥10,987 (−$US 98.74) to ¥25,614 ($US230.20)	NS 0.37
Indirect	¥1,744,903 ($US15,681.70)	¥962,093 ($US8,646.47)	−¥782,810 (−$US7,035.23)	−¥999,271 (−$US8,980.60) to −¥566,349 (−$US5,089.86)	<0.001
Total	¥1,940,421 ($US17,438.85)	¥1,164,924 ($US10,469.34)	−¥775,497 ($US6,969.51)	−¥992,179 (−$US8,916.86) to −¥558,814 (−$US5,017.26)	<0.001
ICER					
Direct/SFD	—	—	¥60.4 ($US 0.52)	¥69.2 (−$US0.56) to ¥307.1 ($US2.76)	N/A
Indirect/SFD	—	—	Dominant[b)]	N/A	N/A
Total/SFD	—	—	Dominant	N/A	N/A
Net benefit	—	—	¥775,497 ($US6,969.51)	¥558,271 ($US5,017.26) to ¥992,179 ($US8,916.86)	N/A

*: Wilcoxon signed-rank test, *a*) Currency exchange for US dollar ($US1=¥111.27, central rate average for 2003/04 published by the Bank of Japan), *b*) Dominant indicates that a new regimen is both clinically and economically superior to an alternative (e.g. pre-introduction). *c*) Net benefit=[incrmntl indirect cost (the absolute value)]-incrmntl direct cost. CI: confidence interval, SFD: Symptom-free day, ICER: incremental cost-effectiveness ratio, NS: not significant, N/A: not available.

800000 yen ($US719) was returned to society annually.

DISCUSSION

Although a number of guidelines documents on asthma treatment and management have been issued in the rest of the world, guidelines for achieving effective asthma control in adults and children in Japan have been published by the Japan Society of Allerology. ICSs are the first-line therapy for asthma control in the guidelines. In Japan, however, ICS utilization rates are low, at approximately 12% for adults and 5% for children (Asthma Insight and Reality in Japan; AIRJ);[14] utilization rates for LABAs are also low. Japanese physicians may generally prefer to oral therapy with agents such as LTRA because of the difficulties associated with instructing on correct inhaler technique. The non-utilization of inhalation therapy

for asthma is associated with significant medical expenditure in Japan for death, hospitalization and emergency room visits associated with asthma exacerbations[15] (monthly expenditure in June 2002 was approximately 20 million yen;[16] $US 180000). In addition, age-adjusted mortality in 2002 was 3.0 per hundred thousand[17] which is approximately 1.5- to 2-fold higher than that in the UK (male: 1.5, female: 2.0),[18] the US (2.0)[19] and Australia (2.0).[20] Other studies[6,21] have shown that combination therapy with ICS/LABA is more cost-effective than oral therapy. However, there have been no studies demonstrating that the ICS/LABA combination is more cost-effective than current oral medication in Japan. Therefore, data from the current study provide the first evidence of the aforementioned effectiveness of ICS/LABA combination for Japan.

In the present study, a comprehensive economic evaluation of the introduction of SLM was performed for the first time in Japan as described previously. This study is considered to fit to validity hierarchy based on the study type of clinical medicine categorized by the Agency for Health Care Policy and Research (AHCPR),[22] i.e., level III of EBM (well-designed observational studies including comparative and correlation studies and case-control studies). Therefore, interpretation of the results is limited by the restricted evidence level and the small number of subjects. However, this study should be valid because it is difficult to conduct meta-analyses, large-scale randomized controlled trials (RCT), or cohort observation studies when the scarcity of clinical medical researchers in Japan is taken into consideration. Moreover, we consider that this study can offer important information in deciding which drugs should be selected at medical institutions practicing primary care given that meta-analyses and RCTs have high internal validity but low external validity and do not directly reflect aspects of clinical practice.[23]

The inclusion of a small number of patients with step 2 asthma in the current study may have influenced the study results. However, patients with step 2 asthma often receive SLM in general practice in order to avoid asthma exacerbations and prevent disease progression, and were therefore included in the analysis.

In this analysis, the cost effectiveness of the introduction of SLM was examined from the payer's perspective and a dominant result of cost reduction in addition to a significant improvement in clinical outcomes (SFDs, SFNs, and PEFs) was obtained for the base case, which was a point estimation. The ICERs, which were calculated because the sensitivity analysis revealed that the introduction of SLM would not necessarily lead to a dominant result, were about 1700 yen ($US15)/SFD and 9800 yen ($US88)/SFN. However, when these ICERs were examined closely, it was found that only a medical cost with an increment of 1700 yen ($US15) or 9800 yen ($US88) was necessary to gain one SFD or SFN even in the worst scenario. Moreover, although a few inferior cases occurred in the examination of imaginary 95% CIs of the two-dimensional normal distribution on the CEP, due to the small number of cases, none showed aggravation of the clinical outcomes in reality. In addition, about 50% of the cases achieved cost reduction, indicating that the combined therapy of ICS and SLM was a superior cost-effective therapy compared to regimens consisting of multiple oral drugs combined with ICS, even taking into consideration that the main reason for the cost reduction was the decreased use of oral drugs represented by LTRAs. Furthermore the stochastic sensitivity analysis using a Monte Carlo Simulation on 10000-time trials revealed that use of SLM is a cost-effective treatment for asthma control in Japanese population.

In the subgroup analysis limited to 33 paid employees, an incremental cost of about 7000 yen ($US63) was evident and, therefore, the ICER was about 60 yen ($US0.5)/SFD. This means that a cost increment of only 60 yen ($US0.5) was necessary to gain one SFD and it is appropriate to introduce SLM from the perspective of a decision maker. On the other hand, as we reported separately,[3] estimation of productivity loss revealed that a statistically significant loss of about 800000 yen ($US719) could be avoided each year. The results of both CEA integrating the cost and productivity loss into the calculation and CBA to estimate the impact on society were very helpful to make a decision, from a societal viewpoint, on the value of adding SLM to ICS therapy. However, the productivity loss in the paid group was estimated by applying standard labor wages categorized according to occupation and gender as shown in a separate report,[3] since retrospective investigation of individual incomes was difficult due to privacy considerations. Therefore, interpretation of the results is limited. However, we consider that the estimation of

productivity loss by the above method is appropriate because a moderate negative correlation ($r=-0.689$, $p<0.001$) was detected between the improvement in SFD, which is a clinical outcome, and evasion of the productivity loss, as reported separately.[3] We also consider that this correlation supports the appropriateness of adopting SFD as the primary end point.

On this basis, the results show that the introduction of SLM is not only cost effective, but also returns a benefit to society that could provide decision makers with sufficient evidence to introduce it into primary care in Japan.

These data support the results of international clinical trials using combination therapy with ICS and SLM.[6,20] Furthermore, as stated in many guidelines, including the GINA, combination therapy with ICS and SLM is essential for the treatment of asthma with a severity≥step 3. It is expected from the results of this analysis that treatment in accordance with the guidelines will also achieve a satisfactory outcome, both clinically and economically, for asthma patients in Japan. Furthermore, if the introduction of ST is approved in Japan in the future, improved compliance is expected as only one inhaler becomes necessary, leading to improved outcomes.

CONCLUSION

The result of this comprehensive economic evaluation of SLM in Japan demonstrates that the introduction of SLM to asthma treatment was cost effective not only from the payer's perspective but also from a societal perspective. Moreover, it was expected that treatment in accordance with guidelines would achieve satisfactory outcomes both clinically and economically in asthma patients in Japan.

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