—Regular Article—

Cost-effectiveness Analysis of Pre-seasonal Medication for Cedar Pollinosis in Japan

Kazuhiro TAMAYAMA,[a,b] Shu-Ling HOSHI,[a] Masahide KONDO,*[,a] and Ichiro OKUBO[a]

[a]*Department of Health Care Policy and Management, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1–1–1 Tennoudai, Tsukuba, Ibaraki 305–8577, Japan, and* [b]*Health and Welfare Division, Yokohama City Totsuka Public Health and Welfare Center, 157–3 Totsuka-cho, Totsuka-ku, Yokohama, Kanagawa 244–0003, Japan*

(Received February 1, 2010; Accepted August 28, 2010)

Pre-seasonal medication is recommended for cases of cedar pollinosis that are expected to manifest severe symptoms during the season, according to the standard clinical guideline in Japan. This study aims to appraise the value for money of additional costs that accompany the choice of pre-seasonal medication from payer's perspective. Based on the 12 reports of controlled clinical trials with Symptom Score (SS) and Medication Score (MS) comparing pre-seasonal medication with intra-seasonal symptomatic medication, 15 incremental cost-effectiveness ratios (ICERs) and 4 integrated ICERs of each group of targeted agents are estimated. Incremental effects are estimated by reading SS charts, and incremental costs are estimated by reading MS charts and using National Health Insurance Medical Fee Schedule and National Health Insurance Drug Price Standard. Estimated ICERs range from ¥322,195 per quality-adjusted life-year (QALY) to ¥57,088,063 per QALY. Integrated ICERs are: ¥1,128,286 per QALY for 2nd generation histamine H_1 receptor antagonists, ¥2,248,018 per QALY for leukotriene receptor antagonists, ¥2,692,911 per QALY for prostaglandin D_2 and thromboxane A_2 receptor antagonists, ¥1,150,943 per QALY for Th2 cytokine suppressors, and ¥1,291,341 per QALY for all agents. Pre-seasonal medication for cedar pollinosis is cost-effective regardless of the choice of the prophylactic agent among 2nd generation histamine H_1 receptor antagonists, leukotriene receptor antagonists, prostaglandin D_2 and thromboxane A_2 receptor antagonists, or Th2 cytokine suppressors, taking the suggested threshold of ¥5,000,000 per 1 QALY gain in Japan. The use of 2nd generation histamine H_1 receptor antagonists and Th2 cytokine suppressors are found more favourable.

Key words——cedar pollinosis; cost-effectiveness; health care expenditure; pre-seasonal medication; seasonal allergic rhinitis (SAR)

INTRODUCTION

Seasonal allergic rhinitis is one of the most prevalent diseases in Japan. The pollen of Japanese cedar that scatters about in the air during the months of January to May is the most common allergen, causing 26.5% of the nation to suffer from cedar pollinosis every year.[1] A remarkably high morbidity raises concern about health care resources used in controlling the disease. Health care expenditure for cedar pollinosis has been estimated at ¥198,600 million[2] to ¥286,000 million[3] annually.

There are several coping strategies and treatment modalities against allergic rhinitis such as patient communication, elimination or avoidance of allergen, medication, specific immunotherapy, and surgical treatment. According to the standard clinical guideline,[4] pre-seasonal oral medication is recommended for cases of cedar pollinosis that are expected to manifest severe symptoms during the season. However, whereas better clinical outcomes are expected, taking pre-seasonal medication for prophylaxis implies a heavier total dose over the season compared to intra-seasonal symptomatic medication.

From the viewpoint of health economics, it is imperative to appraise the value for money of additional costs that accompany pre-seasonal medication. Therefore, we carry out a cost-effective analysis of choosing pre-seasonal medication instead of symptomatic medication in treating cedar pollinosis. The results should inform us whether the choice of pre-seasonal medication is justifiable as an efficient use of finite resources for health care. It would contribute to realise the efficient management of the disease, as well as deepen our understanding of resource implications of preventive care.

MATERIALS AND METHODS

We conduct a cost-effectiveness analysis from the payer's perspective based on the reports of clinical tri-

*e-mail: mkondo@md.tsukuba.ac.jp

als of pre-seasonal medication for cedar pollinosis. Social insurers and patients are regarded as payers.

Comparison We compare the choice of pre-seasonal medication instead of intra-seasonal symptomatic medication with the incremental cost-effectiveness ratio (ICER).

$$ICER = \frac{Incremental\_cost}{Incremental\_effect} = \frac{Cost_{Pre\text{-}seasonal\_treatment} - Cost_{Symptomatic\_treatment}}{Effect_{Pre\text{-}seasonal\_treatment} - Effect_{Symptomatic\_treatment}}$$

Controlled Clinical Trials We carry out a systematic and deliberate literature search of electrical databases: ''Japana Centra Revuo Medicina'' and ''Medline'', with key words such as ''allergic rhinitis'', ''pollinosis'', ''prophylactic'', ''early phase'', or ''pre-seasonal'', which produce 142 reports of controlled clinical trials of medication for cedar pollinosis. Controlled trials comparing pre-seasonal oral medication with intra-seasonal symptomatic oral medication are included in our analysis if the results are reported in a form of Symptom Score (SS) and Medication Score/Symptom-Medication Score (MS/SMS) defined in the latest Japanese Guideline,[4] since SS corresponds to the clinical outcomes or MS/SMS to the health care resource use.

Figure 1 is a flowchart showing the inclusion and exclusion of identified reports of trials. Fifty six trials in accordance with the Japanese Guideline ver. 2 (1994) and earlier, in which SS and MS/SMS are different from one in the latest Japanese guideline ver. 6 (2009) are excluded, since we plan to use SS/MS/SMS in our outcomes estimation and costing. Twenty six trials comparing between agents of pre-seasonal medication or between agents of intra-seasonal symptomatic medication are excluded, since these comparisons are not under our consideration. Four trials of nasal drops or eye drops only are excluded, since only oral medications are recommended for pre-seasonal medication in the guideline. Twenty seven trials not employing SS as a measure of endpoint are excluded from 56 remained trials. Sixteen trials are further excluded, because presented results are not sufficient for our further analysis. Finally, the exclusion of duplicated publication results in the inclusion of 12 trials reports into this study.

The use of SS as a measure of outcomes in the clinical study of cedar pollinosis is recommended in the guideline,[4] and it is used in half of the trials comparing pre-seasonal oral medication with intra-seasonal symptomatic oral medication (29/56: 52%). Al-

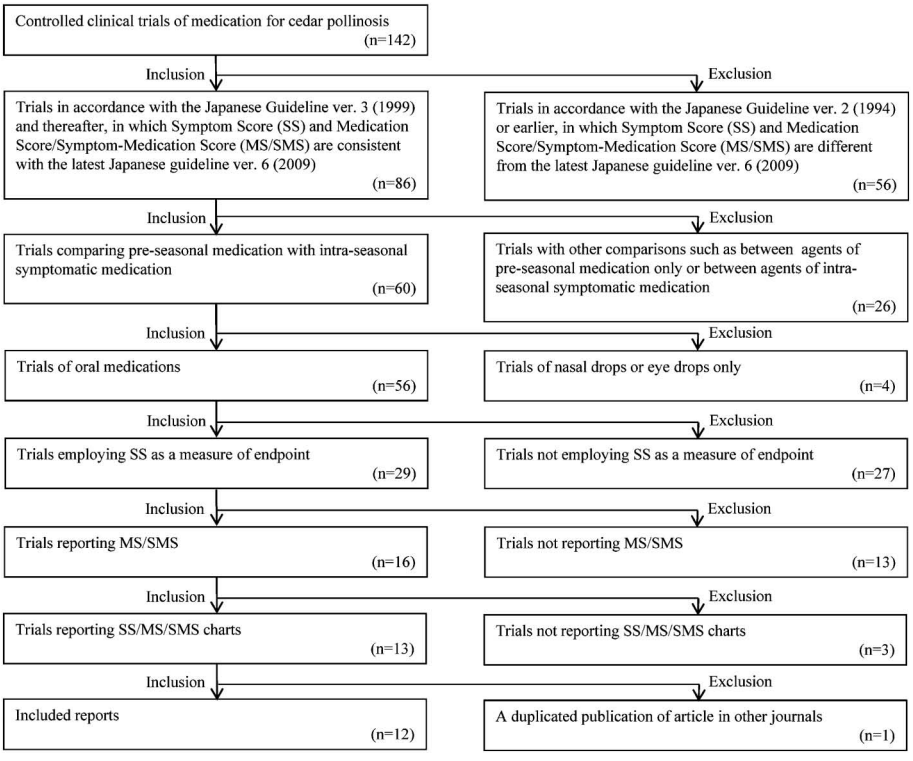


Fig. 1. Inclusion of Reports of Controlled Clinical Trials

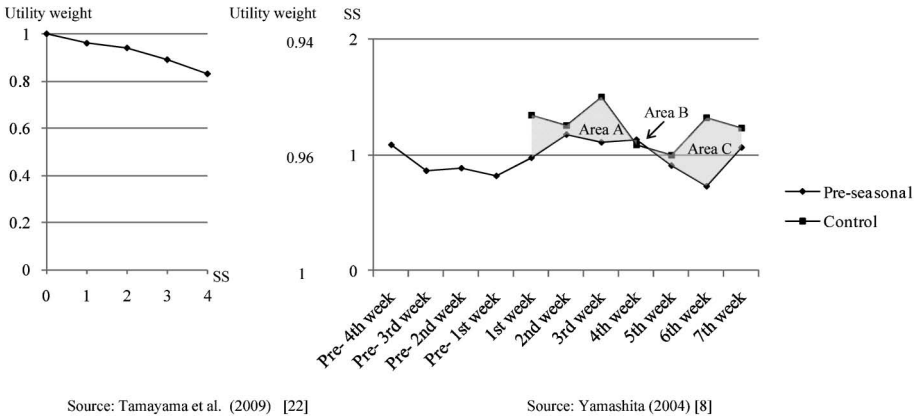
though it is not shown in Fig. 1, about half of the trials not employing SS as a measure of endpoint report sub-scores for SS such as Sneezing Fit Score, Runny Nose Score, or Nasal Congestion Score. This means three quarters of the trials use, or at least partially use, the recommended SS/MS/SMS system. Therefore, we consider that our use of SS/MS/SMS as one of the major inclusion criteria is acceptable, even though the number of finally included reports, twelve, is relatively small. The rest of the trials, about a quarter of all, employ Japanese Rhino-conjunctivitis Quality of Life Questionnaire (JRQLQ),[5] MOS Short-Form 36-Item Health Survey (SF-36),[6] *etc*. as a measure of outcomes.

Table 1 lists twelve identified reports of trials.[7–18] All of them are non-randomised trials, while there is no report of trials with random assignment. The assignment of patients is subject to the timing of patients' voluntary first visit to clinics only, i.e., before or during the season, except Shimizu *et al*. (2005)[15] and Hirata *et al*. (2004),[17] which are three-arm trials with two types of interventions. In Shimizu *et al*. (2005),[15] patients visiting the clinic before the season are assigned to a combined therapy, ''with steroid nasal drop'' group if they were heavily symptomatic in the previous year, or otherwise to a single agent therapy, ''without steroid nasal drop'' group. In Hirata *et al*. (2004),[17] patients visiting the clinic for more than two weeks before the season are assigned to a ''long course'' group, while those visiting less than two weeks before the season are assigned to a ''short course'' group. And Hamajima *et al*. (2006)[13] report two comparisons, one in 2002 season and another in 2006 season. Therefore, we estimate a total of 15 ICERs for all comparisons.

Seven[7–13] report the use of 2nd generation histamine H_1 receptor antagonists; two[14,15] report leukotriene receptor antagonists; one[16] reports prostaglandin D_2 and thromboxane A_2 receptor antagonists; and two[17,18] report Th2 cytokine suppressors as prophylactic agents. As a prior meta-analysis of the effectiveness of pre-seasonal medication summarises effect size by the type of agent,[19] we also estimate integrated ICERs for each group of targeted agent and all agents.

Outcomes Estimation SS is used for calculating incremental effect in terms of quality-adjusted life-years (QALYs). The QALY is one of the recommended measures of outcomes in cost-effectiveness analysis.[20] Especially, its use can be justified when health related quality of life is the important outcome, such as treatment of arthritis, which is expected to have no impact on mortality.[21] In the same way, cedar pollinosis is not a lethal disease and alleviation of unpleasant symptoms is most important in the treatment. Figure 2 illustrates the calculation of incremental effect in terms of QALYs by reading SS charts. Patients' health states during the season measured in SS are converted into utility weights according to Tamayama *et al*. (2009).[22] Outcomes gain is measured as areas between courses followed by the pre-seasonal medication group and the control group during the season.

Incremental effects are integrated for each group of



Source: Tamayama et al. (2009) [22] Source: Yamashita (2004) [8]

Fig. 2. Calculation of Incremental Effect in Terms of QALYs

The right panel is an example of the result of a controlled trial presented with SS chart. Area A and area C show gains in outcomes and area B a loss by pre-seasonal medication. The left panel is a function converting SS to utility weights. We calculate the outcomes gain according to the definition of QALYs: a sum of life years with certain levels of health related quality of life measured in utility weights. Areas A–C in the right panel are measured after the conversion of SS to utility weights based on the left panel as shown in-between the panels. SS; symptom score.

Table 1. Reports of Controlled Clinical Trials of Pre-seasonal Medication Adopted for Cost-effectiveness Analysis

Report	Season	Comparison	Type of agent
Itagaki *et al.* (2003)[7]	2002	65 cases with pre-seasonal olopatadine hydrochloride 5 mg twice a day 72 cases with intra-seasonal symptomatic medication	2nd generation histamine H_1 receptor antagonists
Yamashita (2004)[8]	2002	11 cases with pre-seasonal olopatadine hydrochloride 5 mg twice a day 6 cases with intra-seasonal symptomatic medication	
Hayashi *et al.* (2004)[9]	2003	15 cases with pre-seasonal olopatadine hydrochloride 5 mg twice a day 15 cases with intra-seasonal symptomatic medication	
Yasumoto *et al.* (2004)[10]	2003	29 cases with pre-seasonal olopatadine hydrochloride 5 mg twice a day 75 cases with intra-seasonal symptomatic medication	
Kawauchi *et al.* (2003)[11]	2003	33 cases with pre-seasonal fexofenadine hydrochloride 60 mg twice a day 33 cases with intra-seasonal symptomatic medication	
Ohta *et al.* (2006)[12]	2004	26 cases with pre-seasonal fexofenadine hydrochloride 60 mg twice a day 23 cases with intra-seasonal symptomatic medication	
Hamajima *et al.* (2006)[13]	2002	27 cases with pre-seasonal bepotastine besilate (dosage not stated) 37 cases with intra-seasonal symptomatic medication	
	2006	44 cases with pre-seasonal bepotastine besilate (dosage not stated) 36 cases with intra-seasonal symptomatic medication	
Miyanohara *et al.* (2009)[14]	2005	21 cases with pre-seasonal suplatast tosilate 225 mg twice a day 8 cases with intra-seasonal symptomatic medication	Leukotriene receptor antagonists
Shimuzu *et al.* (2008)[15]	2005	54 cases with pre-seasonal suplatast tosilate 225 mg twice a day 13 cases with pre-seasonal suplatast tosilate 225 mg twice a day & steroid nasal drops (dosage not stated) 26 cases with intra-seasonal symptomatic medication	
Imai *et al.* (2005)[16]	2005	60 cases with pre-seasonal ramatroban 75 mg twice a day 41 cases with intra-seasonal symptomatic medication	Prostaglandin D_2 and thromboxane A_2 receptor antagonists
Hirata *et al.* (2004)[17]	2000–2002	109 cases with pre-seasonal suplatast tosilate 100 mg 3 times a day (long course, $\geq$2 weeks) 57 cases with pre-seasonal suplatast tosilate 100 mg 3 times a day (short course, $<$2 weeks) 52 cases with intra-seasonal symptomatic medication	Th2 cytokine suppressors
Inagawa *et al.* (2007)[18]	2005	67 cases with pre-seasonal suplatast tosilate 100 mg 3 times a day/200 mg twice a day 26 cases with intra-seasonal symptomatic medication	

targeted agent and all agents. Since QALYs are derived from SS chart readings, neither sample level data nor variables representing error are available, any typical statistical model of meta-analysis such as Mantel-Haenszel method, Peto method or Der-Simonian-Laird method are not applicable. We calculate weighted averages based on the total numbers of samples enrolled in each study for the purpose of integration. Ninety five % confidence intervals are also reported.

Costing In the context of this study, costs borne by patients or third party payers such as social insurers are considered. Direct payments to health care providers by them are calculated as costs, while the other type of opportunity costs, such as productivity losses, are left uncounted.

Amounts of health care provided to patients are estimated by reading MS/SMS charts and descriptions of treatments in the reported trials, which are supplemented with the standard treatment suggested by the guidelines at the time of trial. SMS is converted into MS using corresponding SS. Since no monetary data are reported in the 12 reports of controlled clinical trials, we separately estimate unit costs for these according to National Health Insurance Medical Fee Schedule[23] and National Health Insurance Drug Price Standard.[24]

Unit costs, which are multiplied by the amounts of health care provided, are shown in Table 2. Medical fee includes consultation and prescription, which ranges from ¥1,740 to ¥5,547 per consultation depending on the type of consultation and the prescription. For example, it includes the initial visit fee/follow up visit fee, examination fee such as specific IgE test, prescription fee at clinics, and dispensing fee at pharmacies. Additionally, patients are assumed to make a weekly visit for Yamashita (2004),[8] Yasumoto *et al.* (2004),[10] Hamajima *et al.* (2006),[13] Imai *et al.* (2005),[16] and a biweekly visit for Itagaki *et al.* (2003),[7] Hayashi *et al.* (2004),[9] Kawauchi *et al.* (2003),[11] Ohta *et al.* (2006),[12] Miyanohara *et al.* (2009),[14] Shimuzu *et al.* (2008),[15] Hirata *et al.* (2004),[17] Inagawa *et al.* (2007)[18] based on their descriptions in the reports. The proportion of out-of-house prescription is set at 55.1% according to Survey of Medical Care Activities in Public Health Insurance 2008.[25]

Daily drug prices of targeted agents range from ¥126 to ¥296. Prices for additional drugs are calculated as averages of daily prices of possible agents used based on the description in the reports supplemented with the guidelines by the MS/SMS, which range from ¥53 to ¥253.

Incremental costs are integrated for each group of targeted agent and all agents in the similar way as incremental effects. We calculate weighted averages based on the total numbers of samples enrolled in each study. Ninety five % confidence intervals are also reported.

Integrated ICERs In addition to 15 ICERs for all comparisons based on the 12 reports of controlled clinical trials, we calculate integrated ICERs for each group of targeted agent and all agents defined as below:

$$Integrated\_ICER = \frac{Weighted\_average\_of\_Incremental\_costs}{Weighted\_average\_of\_Incremental\_effect}$$

Discounting Since the time horizon of our analysis is one season of cedar pollinosis, which is less than half a year, both effects and costs are not discounted.

Sensitivity Analysis In order to deal with the uncertainty of estimated outcomes and costs, stochastic sensitivity analyses are performed. Assuming that outcomes and costs are subject to triangle distributions, of which bases range ±30% of the estimated value for 15 comparisons and 95% confidence intervals for integrated ICERs, Monte Carlo simulations are carried out with 1,000 iterations.

Effect of Pollen Scattering The association between total pollen counts in the air during the season measured by Durham method and incremental costs/incremental effects/ICERs are also analysed, since it is commonly known that the severity of symptoms and outcomes of treatments depend on the pollen level during the season.[13,17,26] 2nd generation histamine H_1 receptor antagonists and all agents are separately analysed taking the difference in targeted agents into account.

RESULTS

Outcomes Table 3 shows the estimated outcomes. Incremental effects in terms of QALYs are consistently positive, which suggests pre-seasonal medication is more effective compared to intra-seasonal symptomatic medication. Outcome gains range from 0.00007 to 0.00857 QALY. These are equivalent to gaining 37 minutes to 75 days of living in

Table 2. Unit Costs

Medical fee per consultation (¥)

	In-house prescription		Out-of-house prescription
	MS=1	MS≥2	MS≥1
Initial consultation	3,920	3,980	5,547
Follow-up consultation	1,740	1,800	3,367

Drug price per day (¥)

Report	Targeted agent		Additional agent for MS=2		Additional agent for MS=3		Additional agent for MS=4	
Itagaki *et al.* (2003)[7]	olopatadine hydrochloride	139	AAN/AHE/CARE	71	SN/AAN+AHE/AAN+CARE	117	—	—
Yamashita (2004)[8]	olopatadine hydrochloride	139	AAN/AHE/CARE	71	SN/AAN+AHE/AAN+CARE	117	AAN+SE/SN+AHE/SN+CARE/OS/OCAR+AAN+AHE/OCAR+SN/OCAR+SE	131
Hayashi *et al.* (2004)[9]	olopatadine hydrochloride	139	AAN/AHE/CARE	71	SN/AAN+AHE/AAN+CARE	117	—	—
Yasumoto *et al.* (2004)[10]	olopatadine hydrochloride	139	AAN/AHE/CARE	71	SN/AAN+AHE/AAN+CARE	117	—	—
Kawauchi *et al.* (2003)[11]	fexofenadine	178	AAN/AHE/CARE	71	SN/AAN+AHE/AAN+CARE	117	—	—
Ohta *et al.* (2006)[12]	fexofenadine	178	AAN/AHE/CARE	71	SN/SE/PTA+nSN/PTA+nSE/Th2+nSN/Th2+nSE/LA+nSN/LA+nSE	225	2AH+SN/OCAR+SN/SN+AHE/SN+CARE/AHN+SE/SE+OCAR/OS/2AH+AAN+AHE/OCAR+AAN+AHE/2AH+AAN+CARE/OCAR+AAN+OCAR	253
Hamajima *et al.* (2006)[13]	bepotastine besilate	126	2AH/AAN/AHE/CARE	53	2AH+CARE/2AH+AHE/2AH+AAN/SN/SE	65	—	—
Miyanohara *et al.* (2009)[14]	pranlukast hydrate	190	epinastine hydrochloride	79	SN/SE	56	—	—
Shimuzu *et al.* (2008)[15]	pranlukast hydrate	190	AAN/AHE/CARE/2AH	68	SN/SE	56	—	—
	pranlukast hydrate+SN	275	AAN/AHE/CARE/2AH	68	—	—	—	—
Imai *et al.* (2005)[16]	ramatroban	296	bepotastine besilate	126	SN/SE/Th2+nSE/Th2+nSN/LA+nSE/LA+nSN	180	—	—
Hirata *et al.* (2004)[17]	suplatast tosilate	156	AAN/AHE/CARE	210	SN/SE/2AH+AAN/2AH+AHE/2AH+CARE	65	2AH+SN/OCAR+SN/SN+AHE/SN+CARE/SE+AAN/OS/2AH+AAN+AHE/OCAR+AAN+AHE/2AH+AAN+AHE/2AH+AAN+CARE/OCAR+AAN+CARE	60
Inagawa *et al.* (2007)[18]	suplatast tosilate	156	AAN/AHE/CARE/2AH/PTA/LA	127	SN/SE/PTA+nSN/PTA+nSE/LA+nSN/LA+nSE	229	—	—

MS: medication score. SN: steroid nasal drop. AAN: antiallergic nasal drop. AHE: antihistamine eyedrop. CARE: chemical mediator antireleaser eyedrop. 2AH: 2nd generation antihistamine. PTA: Prostaglandin D_2 and thromboxane A_2 receptor antagonist. LA: Leukotriene receptor antagonist. SE: steroid eyedrop. nSE: non-steroid eyedrop. nSN: non-steroid nasal drop. OS: oral steroid. OCAR: oral chemical mediator antireleaser. Th2: Th2 cytokine suppressor

Table 3. Results of Cost-effectiveness Analysis

Report	Weight	Cost (¥) Pre-season (week)	Cost (¥) Intra-season (week)	Incremental cost (¥)	Incremental effect (QALY)	Incremental cost effectiveness ratio: ICER (¥/QALY) (2.5 percentile 97.5 percentile)
Itagaki *et al.* (2003)[7]	137	5,024 (2)	11,459 (6)	2,839	0.00423	671,739 (cost-saving 1,952,966)
			13,643 (6)			
Yamashita (2004)[8]	17	5,388 (4)	11,511 (6)	5,759	0.00080	7,219,096 (1,084,614 14,019,492)
			11,140 (6)			
Hayashi *et al.* (2004)[9]	30	4,955 (1)	11,470 (3)	2,688	0.00230	1,167,904 (cost-saving 3,640,438)
			13,738 (3)			
Yasumoto *et al.* (2004)[10]	104	2,478 (1)	8,281 (6)	1,271	0.00262	485,695 (cost-saving 1,824,704)
			9,488 (6)			
Kawauchi *et al.* (2003)[11]	66	7,810 (4)	11,386 (6)	5,656	0.00578	977,897 (cost-saving 2,079,316)
			13,540 (6)			
Ohta *et al.* (2006)[12]	49	7,810 (4)	11,357 (6)	5,316	0.00455	1,168,498 (cost-saving 2,564,530)
			13,851 (6)			
Hamajima *et al.* (2006)[13] (2002 season)	64	5,261 (3)	8,511 (5)	4,160	0.00007	57,088,063 (2,075,451 126,499,194)
			9,611 (5)			
(2006 season)	80	8,132 (5)	9,924 (6)	7,008	0.00465	1,505,702 (468,257 2,727,413)
			11,047 (6)			
Weighted average of incremental cost & effect [95% confidence interval] and integrated ICER of 2nd generation histamine H_1 receptor antagonists				3,949 [3,787 4,112]	0.00350 [0.00336 0.00364]	1,128,286 (1,076,143 1,179,304)
Miyanohara *et al.* (2009)[14]	29	4,916 (4)	5,760 (4)	6,666	0.00253	2,633,269 (1,530,998 4,028,108)
			4,009 (4)			
Shimuzu *et al.* (2008)[15] (with steroid nasal drop)	39	7,833 (4)	7,247 (4)	5,918	0.00510	1,160,150 (173,793 2,198,236)
			10,941 (4)			
(without steroid nasal drop)	80	8,056 (4)	8,803 (4)	4,139	0.00080	5,188,425 (cost-saving 11,506,374)
			10,941 (4)			
Weighted average of incremental cost & effect [95% confidence interval] and integrated ICER of leukotriene receptor antagonists				5,103 [4,928 5,278]	0.00227 [0.00200 0.00257]	2,248,018 (2,035,549 2,476,613)
Imai *et al.* (2005)[16]	101	5,532 (3)	15,115 (9)	4,452	0.00165	2,692,911 (cost-saving 6,564,557)
			16,195 (9)			
Weighted average of incremental cost & effect [95% confidence interval] and integrated ICER of prostaglandin D_2 and thromboxane A_2 receptor antagonists				4,452 [Not available]	0.00165 [Not available]	2,692,911 (Not available)
Hirata *et al.* (2004)[17] (long course, ≥2 weeks)	109	4,983 (2)	17,225 (10)	2,763	0.00857	322,195 (cost-saving 1,174,346)
			19,445 (10)			
(short course, <2 weeks)	161	7,814 (4)	17,240 (10)	5,609	0.00113	4,964,943 (cost-saving 12,010,133)
			19,445 (10)			
Inagawa *et al.* (2007)[18]	93	10,806 (6)	11,742 (6)	8,479	0.00660	1,285,210 (341,858 2,440,601)
			14,069 (6)			
Weighted average of incremental cost & effect [95% confidence interval] and integrated ICER of Th2 cytokine suppressors				5,490 [5,270 5,710]	0.00477 [0.00442 0.00511]	1,150,943 (1,080,366 1,226,933)
Weighted average of incremental cost & effect [95% confidence interval] and integrated ICER of all agents				4,623 [4,510 4,736]	0.00358 [0.00344 0.00372]	1,291,341 (1,245,606 1,338,728)

perfect health. Weighted averages of each group of targeted agents are: 0.00350 QALY for 2nd generation histamine H_1 receptor antagonists, 0.00227 for leukotriene receptor antagonists, 0.00165 for prostaglandin D_2 and thromboxane A_2 receptor antagonists, 0.00477 for Th2 cytokine suppressors, and 0.00358 for all agents.

Costs Table 3 also shows the estimated costs. Incremental costs are consistently positive as anticipated, which suggests the pre-seasonal medication accompanies additional use of resources for health care. Additional costs range from ¥1,271 to ¥8,479 per season. Weighted averages of each group of targeted agents are: ¥3,949 for 2nd generation histamine H_1 receptor antagonists, ¥5,103 for leukotriene receptor antagonists, ¥4,452 for prostaglandin D_2 and thromboxane A_2 receptor antagonists, ¥5,490 for Th2 cytokine suppressors, and ¥4,623 for all agents.

Here, breakdowns of costs are also presented. In regards to the costs during the season, costs of the pre-medication group are lower than those of the control group, except for Yamashita (2004),[8] Hayashi *et al.* (2004),[9] and Miyanohara *et al.* (2009).[14] These suggest that the pre-seasonal medication tends to reduce resource use during the season.

Cost-effectiveness Table 3 shows the estimated ICERs as well. They range from ¥322,195 per QALY to ¥57,088,063 per QALY. Integrated ICERs of each group of targeted agents are: ¥1,128,286 per QALY for 2nd generation histamine H_1 receptor antagonists, ¥2,248,018 per QALY for leukotriene receptor antagonists, ¥2,692,911 per QALY for prostaglandin D_2 and thromboxane A_2 receptor antagonists, ¥1,150,943 per QALY for Th2 cytokine suppressors, and ¥1,291,341 per QALY for all agents.

Figure 3 plots the results on a cost-effectiveness plane. A threshold line where ICER equals ¥5,000,000 per 1 QALY gain is drawn according to Shiroiwa *et al.* (2010),[27] although there is no established threshold to judge cost-effectiveness in Japan. Three ICERs, Yamashita (2004),[8] Hamajima *et al.* (2006)[13] in the 2002 season, and Shimizu *et al.* (2008)[15] for "without steroid drops" are judged cost-ineffective, and the rest cost-effective. The ICER of Hamajima *et al.* (2006)[13] in the 2002 season, ¥57,088,063 per QALY is remarkably high, which is due to the smallest outcome gain of 0.00007 QALY.

If we take this threshold, the integrated ICERs of 2nd generation histamine H_1 receptor antagonists, leukotriene receptor antagonists, prostaglandin D_2 and thromboxane A_2 receptor antagonists, and Th2 cytokine suppressors are all judged cost-effective. And the integrated ICER of all agents is also judged cost-effective, as well.

Stability of ICERs Table 3 shows the results of stochastic sensitivity analyses. 2.5 percentiles and 97.5 percentiles of 1,000 ICERs obtained by Monte Carlo Simulations are presented along with point esti-

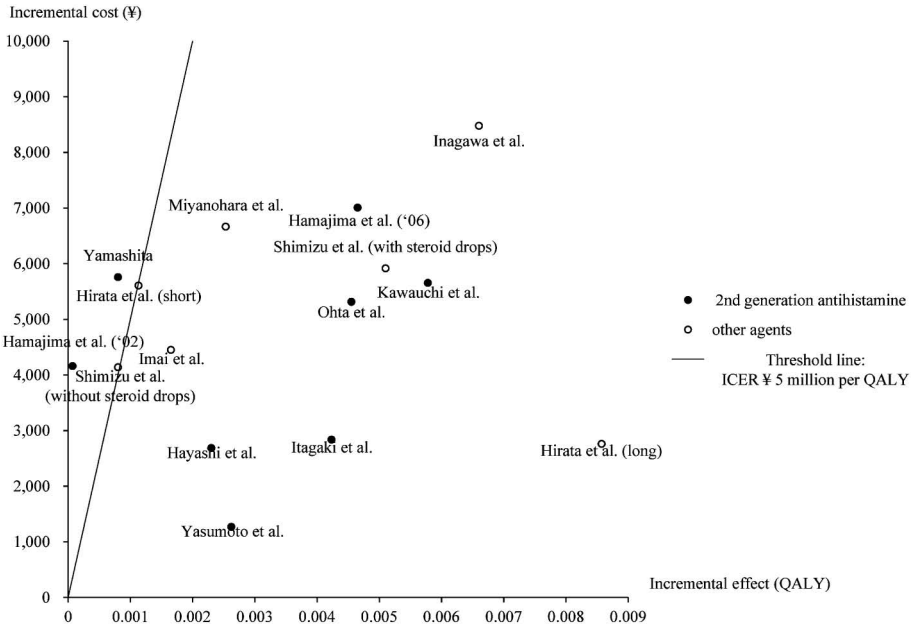


Fig. 3. Cost-effectiveness Plane

mates of ICER. They range from cost-saving, i.e., cost less and gain more, to ¥126,499,194 per QALY. However, only 2 of 97.5 percentiles ICERs, Imai *et al.* (2005),[16] and Hirata *et al.* (2004)[17] for ''short course'', go beyond the suggested threshold of ¥5,000,000 per 1 QALY gain and becoming cost-ineffective by the sensitivity analysis in addition to 3 ICERs, Yamashita (2004),[8] Hamajima *et al.* (2006)[13] in the 2002 season, and Shimizu *et al.* (2008)[15] for ''without steroid drops'', of which estimated ICERs in the base-case analyses have already been judged cost-ineffective.

In regards to the stability of integrated ICERs, no value of 2.5 percentiles results in cost-saving, while no value of 97.5 percentile go beyond the suggested threshold.

Pollen Counts and Incremental Costs/Incremental Effects/ICERs Figure 4 shows the results of correlation analyses between total pollen counts in the air during the season measured by Durham method and incremental costs/incremental effects/ICERs. The scatter diagram in the upper panel illustrates the correlation between total pollen counts and the incremental costs of pre-seasonal medication. Squares of Pearson's correlation coefficient are 0.523 for 2nd generation histamine H_1 receptor antagonists and 0.299 for all agents, both of which are not statistically significant. Similarly, the scatter diagram in the middle panel illustrates the correlation between total pollen counts and the incremental effects. Squares of Pearson's correlation coefficient are 0.088 for 2nd generation histamine H_1 receptor antagonists and 0.057 for all agents, both of which are not statistically significant. And the scatter diagram in the lower panel

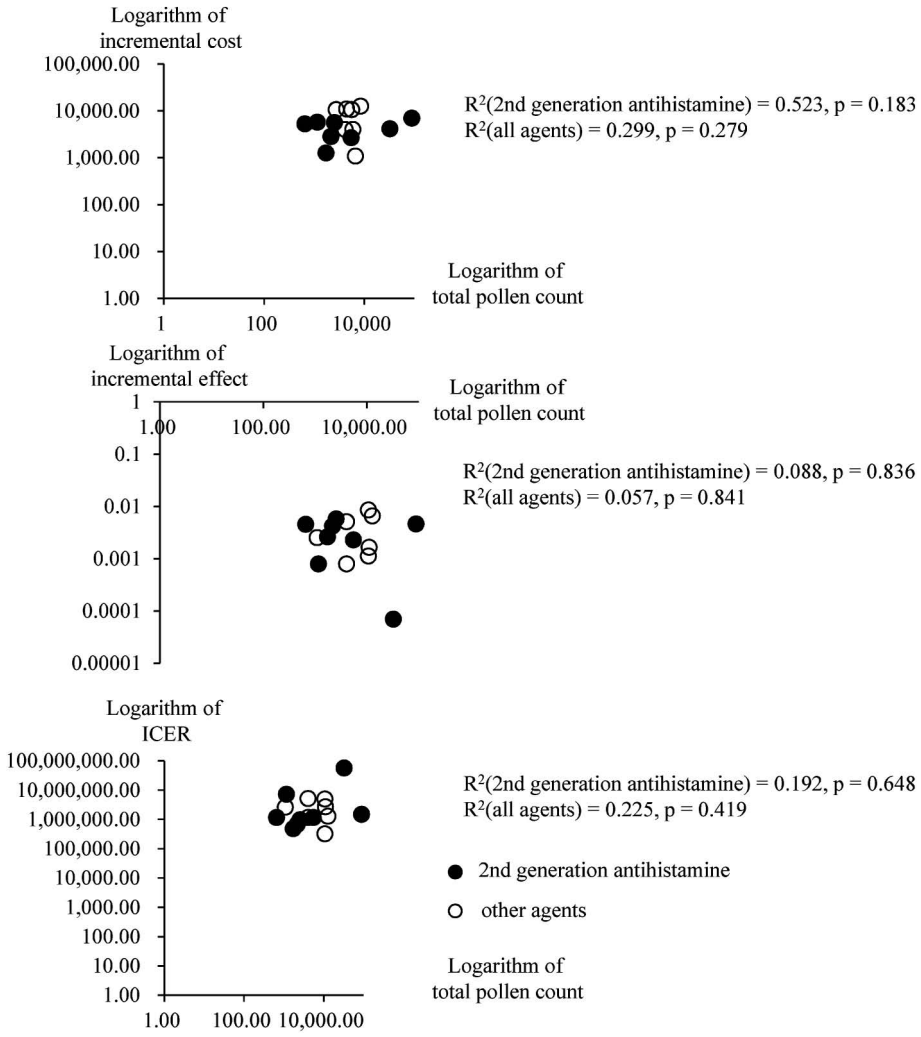


Fig. 4. Correlation between Total Pollen Count and Outcomes/ICERs
ICER; incremental cost-effectiveness ratio.

illustrates the correlation between total pollen counts and the ICERs. Squares of Pearson's correlation coefficient are 0.192 for 2nd generation histamine H_1 receptor antagonists and 0.225 for all agents, both of which are not statistically significant, as well.

DISCUSSION

We conduct a cost-effectiveness analysis of pre-seasonal medication for cedar pollinosis in Japan based on 12 reports of clinical trials, in which not only outcomes but also the resource use are presented. We compare the choice of pre-seasonal medication against intra-seasonal symptomatic treatment with 15 ICERs. The estimated ICERs range from ¥322,195 per QALY to ¥57,088,063 per QALY, and among these, 12 ICERs are less than the suggested threshold for judging cost-effectiveness, ¥5,000,000 per 1 QALY gain.[27] Integrated ICERs of 2nd generation histamine H_1 receptor antagonists of ¥1,128,286 per QALY is judged cost-effective, although 2 out of 8 ICERs are beyond the threshold. Those of leukotriene receptor antagonists of ¥2,248,018 per QALY, prostaglandin D_2 and thromboxane A_2 receptor antagonists of ¥2,692,911 per QALY, Th2 cytokine suppressors of ¥1,150,943 per QALY, and all agents of ¥1,291,341 per QALY are judged cost-effective, as well. These results suggest that the choice of pre-seasonal medication by patients and/or physicians is justifiable as an efficient use of finite resources for health care regardless of the choice of agent. The use of 2nd generation histamine H_1 receptor antagonists and Th2 cytokine suppressors are found more favourable than the use of the other agents from the viewpoint of health economics. The former is mainly due to lower drug costs, and the latter to larger effect among the agents. These results are considered stable, since ranges of ICERs resulted from stochastic sensitivity analyses do not pass beyond the threshold.

Since the suggested threshold for judging cost-effectiveness, ¥5,000,000 per 1 QALY gain,[27] is derived from a survey questioning willingness-to-pay in regards to life threatening diseases, the value may differ for no life threatening disease like cedar pollinosis here. However, we quote this value in this study, because no specific threshold is available in the literature to date and prior cost-effectiveness analyses of pollinosis in developed countries use a threshold similar to ¥5,000,000 per 1 QALY gain.[28,29]

Although we include only two three-arm trials considering prescription patterns, their results imply that limiting target patients with more severe symptoms, administering heavier medication, or prolonging the duration of pre-seasonal medication would make ICERs even more favourable. However, prolonged pre-seasonal medication is not necessary to result in more favourable ICERs among the results based on two-arm trials.

Whereas the association between total pollen counts in the air during the season and outcomes of treatments is known in the literature,[13,17,26] no correlation was found between total pollen counts and incremental costs/incremental effects/ICERs. These may be due to the small number of included reports out of identified controlled clinical trials by our literature search, 12 out of 142, which may have a bias.

There are some points to note as to the method employed in this study. As mentioned above, reports of trials included in this study are so limited that caution is needed in interpreting the results. Arguably, however, our inclusion criteria, reporting in SS and MS/SMS, is one approach to make the most from available knowledge to date in the literature in conducting a cost-effectiveness analysis under the context of this study, since SS allow us to estimate incremental effect in terms of QALYs exactly subject to the definition. And there is no report of trial which describe more detailed resource use than MS/SMS. While it is admittable that estimation of unit costs in our costing is rough, our approach of averaging daily drug prices of possible choice of agents is a reasonably feasible one, and estimated incremental costs successfully reflect the difference in resources used between pre-seasonal medication and symptomatic medication.

Since the significance of productivity losses related to cedar pollinosis has been pointed out,[30,31] leaving this uncounted from our scope of costing might affect the results. Nevertheless, better outcomes by the choice of pre-seasonal medication imply negative incremental productivity loss. Therefore, estimated ICERs might be overestimates.

In conclusion, pre-seasonal medication for cedar pollinosis is cost-effective regardless of the choice of prophylactic agent among 2nd generation histamine H_1 receptor antagonists, leukotriene receptor antagonists, prostaglandin D_2 and thromboxane A_2 receptor antagonists, or Th2 cytokine suppressors.

Acknowledgements This study was financed by a grant from the University of Tsukuba.

REFERENCES

1) Baba K., Nakae K., *Prog. Med.*, **28**, 2001–2012 (2008).
2) Kawaguchi T., Hoshiyama Y., Watanabe Y., Kimura M., *Prog. Med.*, **18**, 2826–2830 (1998).
3) Enomoto M., Satoh Y., *The Medical Frontline*, (Suppl. 12), 269–276 (2003).
4) PG-MARJ Committee, ''Practical Guideline for the Management of Allergic Rhinitis in Japan,'' 6th ed., Life Science, Tokyo, 2009, pp. 1–116.
5) Okuda M., Ohkubo K., Goto M., Okamoto Y., Konno A., Baba K., Ogino S., Enomoto M., Imai T., So N., Ishikawa Y., Takenaka Y., Manndai T., Crawford B., *Acta Oto-Laryngol.*, **125**, 736–744 (2005).
6) Fukuhara S., Bito S., Green J., Hsiao A., Kurokawa K., *J. Clin. Epidemiol.*, **51**, 1037–1044 (1998).
7) Itagaki M., Hori K., Shibahara Y., Sakurada T., Suzuki N., Furukawa N., Kusakari C., *Medical Consultation & New Remedies*, **40**, 857–865 (2003).
8) Yamashita H., *Otologia Fukuoka*, **50**, 230–235 (2004).
9) Hayashi S., Takeuchi K., Yuta A., Tatematsu M., Yoshimura E., Kobayashi M., Sakaida H., Majima Y., *Practica Oto-Rhino-Laryngologica*, **97**, 655–662 (2004).
10) Yasumoto K., Suoya Y., Matsuda S., *J. New Rem. & Clin.*, **53**, 249–256 (2004).
11) Kawauchi H., Kataoka S., Ogasawara K., Ishimitsu R., Tagami N., Murata A., Kimura M., Morikura I., Shimizu Y., Takamura K., Sato, T., Sano K., Nishigori T., Shimizu K., Watanabe K., *Medical Consultation & New Remedies*, **40**, 658–663 (2003).
12) Ohta N., Sakurai S., Yoshitake H., Aoyagi M., *Practica Oto-Rhino-Laryngologica*, **99**, 501–508 (2006).
13) Hamajima Y., Ohno N., Takagi S., Asada T., Niwa Y., Takagi I., Suzuki M., Mamiya S., Moribe K., Watanabe N., Miyamoto N., Hashiba M., Murakami S., *Prog. Med.*, **26**, 1339–1343 (2006).
14) Miyanohara I., Matsune S., Ohori J., Kurono Y., *Otologia Fukuoka*, **55**, 31–38 (2009).
15) Shimizu Y., Kataoka S., Aoi N., Murata A., Kimura M., Sano C., Sano K., Kawauchi H., *JJIAO*, **26**, 23–29 (2008).
16) Imai T., Fujikura T., Arai Y., Yoda K., Kitajima S., Aida M., Ozu C., Sakanushi A., Moriyama H., Endo T., Yoshimura T., Ui N., Okubo K., *Practica Oto-Rhino-Laryngology*, **48**, 427–438 (2005).
17) Hirata K., Komatsu M., Kawai S., Ishitoya J., Ooishi K., Ikema Y., Nagoya T., Kondo N., Enomoto H., Yamaoka H., Kagata H., Saitou Y., Satou H., Komatsu T., Nakagawa C., Kohno H., Gushiken T., Kurihara M., Ito K., Satou M., Takahashi N., Tsukuda M., *Otologia Fukuoka*, **50**, 446–456 (2004).
18) Inagawa S., Nakayama M., Banno T., Go M., Kamazawa T., Eguchi N, Sunagawa H., Tanigawa T., Iwasaki S., Inafuku S., *Practica Oto-Rhino-Laryngologica*, **100**, 769－776 (2007).
19) Nakano K., Okamoto Y., Nakano A., *JJIAO*, **21**, 146–147 (2003).
20) Gold M. R., Siegel J. E., Russell L. B., Weinstein M. C., ''Cost-effectiveness in Health and Medicine,'' Oxford University Press, New York, 1996.
21) Drummond M. F., Sculpher M. J., Torrance G. W., O'Brien B. J., Stoddart G. L., ''Methods for Economic Evaluation of Health Care Programmes,'' 3rd ed., Oxford University Press, Oxford, 2004.
22) Tamayama K., Kondo M., Shono A., Okubo I., *Allergol. Int.*, **58**, 201–207 (2009).
23) Shakaihoken Kenkyujo, ''Ika tensuuhyou no kaishaku. Heisei 20 nen 4 gatsu ban,'' Shakaihoken Kenkyujo, Tokyo, 2008.
24) Jiho., ''Heisei 21 nen 4 gatsu ban. Yakkakijun tensuu hayamihyo,'' Jiho, Tokyo, 2009.
25) Social Statistics Division, Statistics and Information Department, Minister's Secretariat, Ministry of Health, Welfare and Labour, ''Heisei 21 nen shakaiiryou sinryoukouibetsu chosa kekka no gaikyo,'' Ministry of Health, Welfare and Labour, Tokyo, 2009.
26) Takasaki K., Enatsu K., Kumagami H., Takahashi H., *Eur. Arch. Otorhinolaryngol.*, **266**, 673–676 (2009).
27) Shiroiwa T., Sung Y. K., Fukuda T., Lang H.

C., Bae S. C., Tsutani K., *Health Econ.*, **19**, 422–437 (2010).
28) Canonica G. W., Poulsen P. B., Vestenbaek U., *Respir. Med.*, **101**, 1885–1894 (2007).
29) Bachert C., Vestenbaek U., Christensen J., Griffiths U. K., Poulsen P. B., *Clin. Exp. Allergy*, **37**, 772–779 (2007).
30) Nagahama T., *Digest of Science of Labour*, **61**, 166–169 (2006).
31) Okubo K., Kobayashi M., *Allergology & Immunology*, **14**, 218–226 (2007).