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Pharmacoeconomic analysis of DPP-4 inhibitors

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Received March 7, 2013, accepted April 5, 2013

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Pharmazie 68: 909–915 (2013) *doi: 10.1691/ph.2013.3595*

Dipeptidyl peptidase-4 (DPP-4) inhibitors and other incretin-related drugs have attracted attention as antidiabetic agents, but they are expensive. The Japanese government has adopted a policy of reducing healthcare costs, and medical institutions must provide medical care while considering economic efficiency. This study was a comparative survey of the usage, treatment effectiveness, and cost of DPP-4 inhibitors. The subjects were patients prescribed DPP-4 inhibitors (sitagliptin, vildagliptin, and alogliptin) at Gifu Municipal Hospital between February 2010 and August 2011. HbA_{1c}: Japan Diabetes Society values (%) and concomitant antidiabetic agents were surveyed for 12 weeks after the start of DPP-4 inhibitors. A cost-effectiveness analysis showed that the cost required for a 0.1% decrease in HbA_{1c} for 12 weeks was the lowest with vildagliptin (2,478 yen; decrease in HbA_{1c}: $0.75\% \pm 0.85\%$). In a cost analysis with a virtual cohort of 1000 patients, the number of patients who achieved the treatment target (HbA_{1c} 6.5 %) was estimated with respect to a virtual cohort created based on the HbA_{1c} level (7.59 ± 1.13 %) at baseline of 307 patients, in cases assuming the use of each DPP-4 inhibitor. In addition, the incremental cost-effectiveness ratio (ICER) was obtained with sitagliptin 50 mg as the reference. The number of patients achieving the treatment target was the highest with vildagliptin 100 mg (413 of 1000 patients), and the estimated ICER of 28,359 yen was the lowest. Robustness was also confirmed with a sensitivity analysis. These results suggest that vildagliptin provides a superior cost-benefit.

1. Introduction

The number of diabetes mellitus (DM) patients has been increasing dramatically in recent years. In Japan, the total number of DM patients in 2008 was 2.37 million according to the Ministry of Health, Labour and Welfare (http://www.mhlw.go.jp/toukei/saikin/hw/kanja/08/index.html). The Ministry also announced that the cost for diabetes treatment was 1.19 trillion yen out of the total national healthcare cost of 34.8 trillion yen (http://www.mhlw.go.jp/toukei/saikin/hw/k-iryohi/08/index.html). In a plan to moderate healthcare costs (5-year plan) that began in fiscal year 2008, the Ministry set official targets and began working to promote moderation of rising healthcare costs with a main emphasis on prevention of lifestyle-related diseases, including diabetes, and optimization of healthcare costs (http://www.mhlw.go.jp/topics/2005/10/tp1019-1b.html).

Medical costs for diabetes tend to be higher than for other lifestyle-related diseases (Oishi et al. 2004), and in Japan, there is an overwhelmingly greater proportion of type 2 DM patients, for whom drug costs account for the largest proportion of outpatient medical fees (Kanatsuka et al. 2006). Decreased ability to secrete insulin together with worsening of insulin resistance have a large effect in Japanese DM patients, the cause of which is thought to be attrition of pancreatic β cells. Insulin preparations and oral hypoglycemic agents (OHA) are drug treatments of choice for type 2 diabetes. With insulin preparations, blood glucose can be controlled by selecting a preparation suited to the patient from among preparations that include rapid-acting and long-acting types. However, there are also problems with insulin preparations, including a troublesome injection technique, higher cost than for OHA, and further accumulation of costs with injection needles and devices for self-monitoring of blood glucose. With OHA, the basic treatment is centered on biguanides (BG) and sulfonylureas (SU), with addition as appropriate of thiazolidine (TZD) derivatives, α-glucosidase inhibitors (α-GI), or other insulin-sensitizing agents depending on the patient's condition (diabetes treatment guidelines of the Japan Diabetes Society). The first-line drugs BG and SU have been used for many years and have a large hypoglycemic effect. Problems such as severe lactic acidosis with BG and pancreatic β cell attrition, hypoglycemia, weight increase, and secondary failure with SU have been noted, and medical costs to deal with these problems must also be considered. Additional drug costs are also likely when combination antihypertensive or antihyperlipidemic agents are used to prevent diabetic complications.

In Japan, the dipeptidylpeptidase-4 (DPP-4) inhibitor sitagliptin was launched in 2009 as an antidiabetic agent with a new mechanism of action. Incretin, which consists of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), is broken down by DPP-4 in a short time. Raising the concentration of incretin in blood by inhibiting DPP-4 can enhance the secretion of insulin. Sitagliptin and other DPP-4 inhibitors are reported to decrease the likelihood of

hypoglycemia and weight gain during their administration, as well as provide stable glycemic control (Iwamoto et al. 2010; Kikuchi et al. 2009). They are predicted to be used with greater frequency in the future. However, among antidiabetic agents, DPP-4 inhibitors are particularly expensive, and while moderation in healthcare costs is being promoted, treatments and medications will be increasingly selected with a view to economic efficiency in the coming years.

Cost-utility analysis is often used in pharmacoeconomic assessments, and comparisons of treatment effectiveness and cost have been made between conventional antidiabetic agents (Ikeda and Kobayashi 2010; Pscherer et al. 2010). Comparisons have also been made with incretin-related drugs (Davies et al. 2012). However, while studies on different DPP-4 inhibitors have compared treatment effectiveness (Koide and Yamazaki 2010; Sakamoto et al. 2012), there have been no reports on their economic aspects. In this study, treatment effectiveness and cost of DPP-4 inhibitors were compared using a cost-effectiveness analysis that calculated the cost per unit of effect in a cost-benefit analysis. A cost analysis based on a virtual cohort of 1000 patients, as reported by Wilson et al. (2003), was also performed.

2. Investigations and results

2.1. Treatment effectiveness and cost analysis of DPP-4 inhibitors

HbA_{1c} (Japan Diabetes Society values) trends in patients prescribed DPP-4 inhibitors are shown in Table 1. HbA_{1c} data for 240 patients were extracted from among patients who received sitagliptin for 12 weeks or more. With sitagliptin, HbA_{1c} decreased from $7.61 \pm 1.10\%$ (mean $\pm$ standard deviation) at baseline to $6.84 \pm 0.79\%$ at 12 weeks. Similarly, HbA_{1c} declined with vildagliptin (37 patients) and alogliptin (30 patients). The results of combination treatment for 12 weeks in these patients are shown in Table 2.

Next, a cost analysis was done with the decrease level in HbA_{1c} as the reference (Table 3). From Table 1, the decrease level in HbA_{1c} at 12 weeks from baseline was 0.78 ± 0.89 % with sitagliptin, 0.75 ± 0.85 % with vildagliptin, and 0.74 ± 1.22 % with alogliptin. No significant difference in the HbA_{1c} decrease level was seen among the three agents. The cost of sitagliptin was calculated to be 301 yen per day and a total of 25,322 yen for 12 weeks. Similarly, the cost of vildagliptin was 221 yen per day and 18,548 yen for 12 weeks, the least expensive of the three. In contrast, alogliptin was the most expensive, at 355 yen per day and 29,840 yen for 12 weeks. The amount needed for a 0.1% reduction in HbA_{1c} for 12 weeks was calculated to be 3,261 yen for sitagliptin, 2,478 yen for vildagliptin, and 4,023 yen for alogliptin. Thus, the cost was the lowest with vildagliptin.

2.2. Cost analysis with a virtual cohort of 1000 patients

2.2.1. Treatment efficacy in trials

An analysis was performed of the DPP-4 inhibitors sitagliptin 50 mg and 100 mg, vildagliptin 50 mg and 100 mg, and alogliptin 25 mg. First, a base case was established, and the analysis was done. As shown in Table 4, the decrease level in HbA_{1c} (mean $\pm$ standard deviation) for 12 weeks obtained from clinical trials was largest with vildagliptin 100 mg.

2.2.2. Treatment effectiveness in virtual cohort

The mean value and standard deviation for HbA_{1c} was 7.59 ± 1.135 % at baseline for 307 patients who received the three DPP-4 inhibitors at Gifu Municipal Hospital for 12 weeks (Table 1). Using a normal distribution for this value, HbA_{1c} was hierarchized at 0.1% intervals, and a virtual cohort was created with 1000 patients between 6.5% and 9.0%. The decrease value needed for HbA_{1c} to reach 6.5% in each band was determined, and patient distributions as in Table 5(1) were obtained.

Next, the number of patients in whom HbA_{1c} reached 6.5% at 12 weeks when each of the drugs was used in the virtual cohort of 1000 patients was calculated (Table 5(2)). The number of patients who achieved the target HbA_{1c} of 6.5% was 412.95 of the 1000 patients with vildagliptin 100 mg (two 50 mg tablets), which was the highest. With sitagliptin, the numbers shows no difference.

2.2.3. Comparison of cost and cost-effectiveness

As shown in Table 6(1), the cost when DPP-4 inhibitors were used for 12 weeks in the virtual cohort of 1000 patients was the highest with sitagliptin 100 mg, followed by vildagliptin 100 mg, alogliptin 25 mg and sitagliptin 50 mg. Vildagliptin 50 mg was the least expensive.

Next, the additional drug cost and incremental number of patients who achieved the treatment target were calculated when sitagliptin 50 mg, which is most commonly prescribed at Gifu Municipal Hospital, was taken as the reference (Table 6(2)). With sitagliptin 100 mg, the incremental number of patients that achieved the treatment target was only 1.46, even though the cost doubled. With vildagliptin 50 mg, the cost was kept to 6,267,240 yen, but the number of patients achieving the target also decreased by 10.62 patients. With vildagliptin 100 mg, an additional 89.13 patients were able to reach the target with an additional drug cost of 2,527,560 yen. With alogliptin, the incremental number of patients was 24.76, with an additional drug cost of 2,527,560 yen. A comparison of the incremental cost-effectiveness ratio (ICER) revealed that, with vildagliptin 100 mg, an increase of one patient could be obtained with the lowest additional drug cost of 28,359 yen/person. This was followed by alogliptin 25 mg at 102,062 yen/patient. The highest ICER was 9,188,822 yen/patient with sitagliptin 100 mg.

2.2.4. Sensitivity analysis

To confirm the robustness of the base case analysis results, the ICER was calculated when the standard deviation of the HbA_{1c} decrease effects for each drug was changed from the clinical trial value to 0.1 and 1.0. For example, the decrease level in HbA_{1c} with sitagliptin 50 mg was $0.70\% \pm 0.58\%$, but in the sensitivity analysis it was calculated as $0.70 \pm 0.10\%$ or $0.70 \pm 1.00\%$. Compared with the base case (Table 6(2)), when the standard deviation was 0.1%, the difference among all drugs in the number of patients that achieved the target widened, and the incremental number of patients who achieved the treatment target increased with sitagliptin 100 mg, vildagliptin 100 mg, and alogliptin 25 mg. At the same time, ICER decreased (Table 7(1)). When the standard deviation was 1.0%, the difference in the incremental number of patients who achieved the target became smaller, and ICER increased (Table 7(2)). In either case, the ICER with vildagliptin 100 mg was the lowest, and there was no change in ranking.

Costs were also calculated using the revised drug prices in the revised medical fee schedule of fiscal year 2012 (Table 8). The number of patients who achieved the treatment target of HbA_{1c} 6.5% (Table 5(2)) was used in the base case for treatment effectiveness. The ICER decreased with the decrease in price of each drug, but the ICER was the lowest with vildagliptin 100 mg, and no change in ranking was seen (Table 8(2)).

3. Discussion

The comparison of the effects of DPP-4 inhibitors showed the largest decrease in HbA_{1c} in patients using sitagliptin. The

Table 1: HbA_{1c} trends with DPP-4 inhibitors

Treatment	Change of HbA_{1c} (%) in the DPP4-inhibitor (mean ± standard deviation)			
	Baseline	4 weeks	8 weeks	12 weeks
Sitagliptin (n = 240)	7.61 ± 1.10	7.25 ± 0.89	6.97 ± 0.78	6.84 ± 0.79
Vildagliptin (n = 37)	7.46 ± 1.35	7.09 ± 1.11	6.83 ± 1.00	6.71 ± 0.91
Alogliptin (n = 30)	7.59 ± 1.10	7.17 ± 0.88	6.90 ± 0.80	6.85 ± 0.78

HbA_{1c} (%): Japan Diabetes Society values

Table 2: Combination drug prescriptions at 12 weeks

	Sitagliptin 50 mg (n = 240)	Vildagliptin 50 mg (n = 37)	Alogliptin 25 mg (n = 30)
	The prescription number (%) of patients		
One tablet	236 (98.3%)	9 (24.3%)	29 (96.7%)
Two tablets	2 (0.8%)	28 (75.7%)	–
Three tablets	1 (0.4%)	–	–
Half tablet	1 (0.4%)	–	1 (3.3%)
the combination drugs			
0 (single drug)	53 (22.1%)	21 (56.8%)	5 (16.7%)
One drug	95 (39.6%)	10 (27.0%)	10 (33.3%)
Two drugs	57 (23.8%)	4 (10.8%)	6 (20.0%)
Tree drugs	27 (11.3%)	2 (5.4%)	8 (26.7%)
Four drugs	8 (3.3%)	–	1 (3.3%)
Number of the prescriptions			
Kind of the concomitant drugs			
Sulfonylurea	95	11	14
Biguanide	86	8	15
α-Glucosidase inhibitor	65	3	13
Thiazolidinedione	45	2	8
Insulin	31	–	–

Table 3: HbA_{1c} decrease value and cost analysis with DPP-4 inhibitors

Treatment	Decrease level in HbA_{1c} (%) (mean ± SD) (A)	Drug cost (yen)		
		The daily cost[a)] (yen) (B)	Total cost of 12 weeks (yen) (c)	Cost for decrease in HbA_{1c} 0.1% (yen) (D)
Sitagliptin (n = 240)	0.78 ± 0.89	301	25,322	3,261
Vildagliptin (n = 37)	0.75 ± 0.85	221	18,548	2,478
Alogliptin (n = 30)	0.74 ± 1.22	355	29,840	4,023

a) Using revised drug prices of April 2011 in Japan
(A) Decrease level of HbA_{1c} (%) at 12 weeks
(B) Drug price per tablet or per unit × dose of DPP-4 inhibitor and combination drugs
(C) Daily drug cost (B) × 84 (days)
(D) (Total drug cost for 12 weeks (C)) / (Decrease level in HbA_{1c} (A)) / 0.1)
No significant difference is seen in the decrease level in HbA_{1c} among the three drugs.

Table 4: Decrease level in HbA_{1c} of clinical trials after use of DPP-4 inhibitors (after 12 weeks)

Treatment	Dose	HbA_{1c} (%) (mean ± SD)	
		Baseline	Decrease level in 12 weeks
Sitagliptin	50 mg 1 tablet	7.57 ± 0.84	0.70 ± 0.58
	100 mg 1 tablet	7.56 ± 0.80	0.71 ± 0.55
Vildagliptin	25 mg 2 tablets	7.40 ± 0.90	0.67 ± 0.59
	50 mg 2 tablets	7.40 ± 0.80	0.92 ± 0.61
Alogliptin	25 mg 1 tablet	7.48 ± 0.99	0.77 ± 0.54

HbA_{1c} decrease effect was also larger with vildagliptin than with alogliptin. In a reported meta-analysis comparison of sitagliptin and alogliptin (Koide and Yamazaki 2010), a larger decrease in HbA_{1c} was also seen with sitagliptin than with alogliptin, but there were problems, including a large difference in the amount of data for each drug and inconsistency in combination drugs. In

Table 5: Distribution of people in the virtual cohort of 1000 patients

(1) Number of virtual patients at baseline

HbA_{1c} level (%) of the baseline	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0
The decrease level in HbA_{1c} needed to reach 6.5%	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2	2.3	2.4	2.5
No. of patients per 1000	30	32	35	37	39	41	43	45	46	47	47	47	47	47	46	44	43	41	39	37	34	32	29	27	24	22

(2) Number of patients estimated to have achieved the treatment target (HbA1c 6.5) after 12 weeks

Treatment	Dose	No. of patients achieved treatment target:HbA_{1c} 6.5%
Sitagliptin	50 mg	323.82
	100 mg (two tablets of 50 mg)	325.46
Vildagliptin	50 mg	313.20
	100 mg (two tablets of 50 mg)	412.95
Alogliptin	25 mg	348.59

Table 6: Drug cost and incremental cost-effectiveness ratio of DPP-4 inhibitors in the virtual population of 1000 patients

(1) Drug cost

Treatment	Dose	Drug cost (yen)		
		The daily cost (A)	Total cost in 12 weeks (B)	Total cost in 12 weeks of 1000 patients (C)
Sitagliptin	50 mg	179.31	15,062	15,062,040
	100 mg (two tablets of 50 mg)	358.62	30,124	30,124,080
Vildagliptin	50 mg	104.70	8,795	8,794,800
	100 mg (two tablets of 50 mg)	209.40	17,590	17,589,600
Alogliptin	25 mg	209.40	17,590	17,589,600

Drug cost for 12 weeks = Daily drug cost × 84 (days)
Drug cost for 12 weeks for 1000 patients = Drug cost for 12 weeks × 1000 (patients)

(2) Incremental cost-effectiveness ratio with sitagliptin 50 mg as reference

Treatment	Dose	Virtual cohort of 1000 patients				
				Incremental cost -effectiveness ratio to sitagliptin 50 mg		
		Total cost in 12 weeks (yen)	No. of patients achieved treatment target:HbA_{1c} 6.5%	Additional drug cost in 12 weeks (yen) (A)	Incremental no. of patients achieved treatment target (B)	ICER [a] (A/B)
Sitagliptin	50 mg	15,062,040	323.82	–	–	–
	100 mg	30,124,080	325.46	15,062,040	1.64	9,188,822
Vildagliptin	50 mg	8,794,800	313.20	–6,267,240	–10.62	(589,859)
	100 mg	17,589,600	412.95	2,527,560	89.13	28,359
Alogliptin	25 mg	17,589,600	348.59	2,527,560	24.76	102,062

a) ICER: Incremental cost-effectiveness ratio

a crossover trial that compared sitagliptin 50 mg and vildagliptin 100 mg (Sakamoto et al. 2012), vildagliptin 100 mg was found to produce a larger decrease in HbA_{1c} (no significant difference). In the present study, the assessment of treatment effectiveness included combination drugs, and so comparisons under the same conditions are difficult. In the future, it will be necessary to compare patients with combined use of a specific OHA or with single drugs only.

In this study, drug cost alone was used for the analysis of costs. Based on cost-effectiveness analysis, a comparison was made of the cost required to decrease HbA_{1c} 0.1% as a unit of effect, and vildagliptin was shown to be the least expensive. The next highest cost-benefit was with sitagliptin, which is used most frequently and in the largest number of patients.

Cost is also expected to be greatly affected by combination drugs. The cost with sitagliptin especially, which tends to be used in more patients with combination insulin preparations than other drugs (31 of 240 patients), is thought to increase readily. However, in a comparison of sitagliptin and alogliptin, the cost for alogliptin was higher. This is thought to be because

Table 7: Sensitivity analysis: With changes in the standard deviation[a)] of the decrease level in HbA1c of clinical trials

(1) Incremental cost-effectiveness ratio when standard deviation is taken to be 0.10%

		Virtual cohort of 1000 patients				
				Incremental cost -effectiveness ratio to sitagliptin 50 mg		
Treatment	Dose	Total cost in 12 weeks (yen)	No. of patients achieved treatment target [b)]:HbA_{1c} 6.5%	Additional drug cost in 12 weeks (yen) (A)	Incremental no. of patients achieved treatment target (B)	ICER (A/B)
Sitagliptin	50 mg	15,062,040	302.17	–	–	–
	100 mg	30,124,080	306.68	15,062,040	4.51	3,340,178
Vildagliptin	50 mg	8,794,800	288.71	− 6,267,240	–13.45	(465,794)
	100 mg	17,589,600	403.55	2,527,560	101.39	24,930
Alogliptin	25 mg	17,589,600	333.97	2,527,560	31.80	79,486

a) Decrease level at 12 weeks from Table 4
b) No. of patients who achieved the treatment target when the standard deviation is 0.10%

(2) Incremental cost-effectiveness ratio when the standard deviation is taken to be 1.00%

		Virtual cohort of 1000 patients				
				Incremental cost -effectiveness ratio to sitagliptin 50 mg		
Treatment	Dose	Total cost in 12 weeks (yen)	No. of patients achieved treatment target [C)]:HbA_{1c} 6.5%	Additional drug cost in 12 weeks (yen) (A)	Incremental no. of patients achieved treatment target (B)	ICER (A/B)
Sitagliptin	50 mg	15,062,040	365.44	–	–	–
	100 mg	30,124,080	372.22	15,062,040	6.78	2,222,191
Vildagliptin	50 mg	8,794,800	357.06	− 6,267,240	–8.38	(748,166)
	100 mg	17,589,600	430.60	2,527,560	65.16	38,788
Alogliptin	25 mg	17,589,600	385.24	2,527,560	19.80	127,656

c) No. of patients who achieved the treatment target when the standard deviation is 1.00 %

Table 8: Sensitivity analysis: Drug cost and incremental cost-effectiveness ratio with revised drug prices of April 2012 in Japan

(1) Drug cost

		Drug cost (yen)		
Treatment	Dose	The daily cost (A)	Total cost in 12 weeks (B)	Total cost in 12 weeks of 1000 patients (C)
Sitagliptin	50 mg	166.00	13,944	13,944,000
	100 mg (two tablets of 50mg)	332.00	27,888	27,888,000
Vildagliptin	50 mg	97.50	8,190	8,190,000
	100 mg (two tablets of 50mg)	195.00	16,380	16,380,000
Alogliptin	25 mg	207.80	17,455	17,455,200

Drug cost for 12 weeks = Daily drug cost × 84 (days)
Drug cost for 12 weeks for 1000 patients = Drug cost for 12 weeks × 1000 (patients)

(2) Incremental cost-effectiveness ratio with sitagliptin 50 mg as reference

		In vertual cohort of 1000 patients				
				Incremental cost -effectiveness ratio to sitagliptin 50 mg		
Treatment	Dose	Total cost in 12 weeks (yen)	No. of patients achieved treatment target:HbA_{1c} 6.5%	Additional drug cost in 12 weeks (yen) (A)	Incremental no. of patients achieved treatment target (B)	ICER (A/B)
Sitagliptin	50 mg	13,944,000	323.82	–	–	–
	100 mg	27,888,000	325.46	13,944,000	1.64	8,506,745
Vildagliptin	50 mg	8,190,000	313.20	− 5,754,000	–10.62	(541,554)
	100 mg	16,380,000	412.95	2,436,000	89.13	27,332
Alogliptin	25 mg	17,455,200	348.59	3,511,200	24.76	141,781

the unit price of alogliptin is high and is affected by the relatively large proportion of patients with two or more combination drugs. With vildagliptin, a factor that keeps drug costs down is the large proportion of cases in which it is used alone.

In the cost analysis with the virtual cohort of 1000 patients, the incremental number of patients who achieved the treatment target increased in the same order as that for treatment effectiveness obtained from clinical trial data in the base case analysis. Additional drug costs were also kept down. The order did not change in the sensitivity analysis, and robustness was maintained. In this study, the number of patients who used each of the DPP-4 inhibitors alone at the same dose for at least 12 weeks at Gifu Municipal Hospital was small, and so they could not be compared with the virtual cohort. In the future it will be necessary to increase the amount of data for a comparative investigation. In addition, analysis with a more realistic model will be possible by adopting more realistic usage trends for each drug according to the number of patients with each dose and conducting analyses that incorporate various patterns, including cases such as when combination drugs are used under the same conditions as in clinical trials.

Many studies using cost-utility analysis are conducted in pharmacoeconomic cost-benefit analyses. Cost-utility analysis uses quality adjusted life years (QALY), which includes changes in QOL with adverse effects from treatments and progression of symptoms as indicators of effectiveness. In addition to drug costs, the cost often includes treatment costs for complications if patients have diabetes. Many reports on cost analysis for diabetes also mention conditions such as dyslipidemia and hypertension (Palmer et al. 2004; Desaki et al. 2010). From overall evaluation of lifestyle-related diseases or evaluation of the effects of test values, it is seen that clinical data are widely used. The number of reports on incretin-related drugs is also increasing, and it is anticipated that many institutions will perform survey studies in the future.

This study focused only on HbA_{1c} for treatment effectiveness based on a cost-effectiveness analysis, and for cost it looked only at drug cost with regard to diabetes treatment. In a comparison of data obtained in actual clinical settings and data obtained in clinical trials, the same trends were seen for cost-benefit, even though the combination drugs and detailed conditions differed. From the results of actual treatment effectiveness and drug cost analysis in Gifu Municipal Hospital and cost analysis in the virtual cohort, it was found that, among the three DPP-4 inhibitors (sitagliptin, vildagliptin, and alogliptin), vildagliptin 100 mg was superior in terms of cost-effectiveness. Use of these study results can improve drug treatment while achieving economic efficiency.

4. Experimental

4.1. Survey subjects

The subjects were patients who were prescribed DPP-4 inhibitors during inpatient or outpatient treatment at Gifu Municipal Hospital between February 2010 and July 2012.

4.2. Survey items

Age, sex, use of DPP-4 inhibitors, use of antidiabetic agents other than DPP-4 inhibitors, and HbA_{1c} were obtained from electronic medical records. The observation period was 12 weeks from the first DPP-4 inhibitor prescription.

4.3. Treatment effectiveness and cost analysis of DPP-4 inhibitors

4.3.1. Treatment effectiveness

The main outcome of treatment effectiveness was HbA_{1c}, which was compared for the different DPP-4 inhibitors. Changes in HbA_{1c} of patients who used each DPP-4 inhibitor continuously for 12 weeks from the start of administration without change in the prescription were examined.

4.3.2. Cost analysis

In the cost analysis, only the drug cost was examined in relation to diabetes treatment, using the revised drug prices of April 2011 in Japan. For the above-mentioned patients, the cost for DPP-4 inhibitors and combination drugs (drug price per tablet or unit for each drug × dose) was assumed to be the price per day, and it was multiplied by 84 (days) to calculate the drug cost for 12 weeks. The compliance of the subjects in this study was good regardless of whether they were inpatients or outpatients, and the amount of each drug taken was assumed to be the same as the number of days prescribed.

4.4. Cost analysis with a virtual cohort of 1000 patients

4.4.1. Treatment effectiveness

The following procedures were followed to calculate the cost for the base case.

1) The HbA_{1c} decrease effect (mean decrease ± standard deviation) for 12 weeks was obtained from dose-response trials of sitagliptin and vildagliptin (Iwamoto et al. 2010; Kikuchi et al. 2009) and dose-finding studies of alogliptin (in-house data) with Japanese subjects. Among the doses actually prescribed in Gifu Municipal Hospital, trial results were examined for sitagliptin and vildagliptin 50 mg or 100 mg, and alogliptin 25 mg.

2) The patient distribution was estimated on the assumption of a normal distribution, using the mean value and standard deviation for HbA_{1c} at baseline in the patients taken as subjects of the treatment effectiveness and cost analysis of DPP-4 inhibitors. From among them, a virtual cohort of patients was created when the number of patients in the distribution of HbA_{1c} of 6.5% or more increased to 1000.

3) The target value used for HbA_{1c} was 6.5%, a level at which glycemic control is judged to be possible in the diabetes treatment guidelines. HbA_{1c} values were hierarchized every 0.1%, and the level of decrease needed for the virtual patient number and to make HbA_{1c} 6.5% in each band at baseline was obtained.

4) When the respective drugs for the virtual cohort of 1000 patients were used, the HbA_{1c} decrease effect was assumed to be distributed with the decrease values and standard deviations obtained in the trials in all bands at baseline. The number of people who achieved the target HbA_{1c} value of 6.5% after 12 weeks (number of patients who achieved the target) was then calculated with this distribution. The difference between the number of patients who achieved the target with each drug and the number who achieved the target with the sitagliptin 50 mg standard was obtained as the incremental number of patients who achieved the treatment target.

4.4.2. Cost and cost-effectiveness ratio

The cost for treatment was taken to be the drug cost for 12 weeks, using the revised drug prices of April 2011 in Japan. The drug cost was obtained by multiplying the drug price per tablet in the daily dose by 84 (days). Sitagliptin is sold in standard tablets of 50 mg and 100 mg, but the standard tablet used at Gifu Municipal Hospital is 50 mg, and so the drug price of 100-mg tablets was calculated as two 50-mg tablets. Since vildagliptin is sold only in a 50-mg standard tablet, 100 mg was calculated as two 50-mg tablets.

As with the incremental number of patients who achieved the treatment target, the difference in the total cost for 12 weeks of each drug and the sitagliptin 50 mg reference was determined as the additional drug cost. The ICER obtained by dividing the additional drug cost by the incremental number of patients who achieved the treatment target, was compared for each drug.

ICER (yen/person) = Additional drug cost (yen) / Incremental no. of patients who achieved the treatment target (persons)

4.4.3. Sensitivity analysis

To confirm the robustness of the results for the base case, the effects were investigated when the standard deviation (Table 4) in the level of the HbA1c decrease effect with each drug was changed to 0.1% and 1.05, and when each drug was changed to the revised medical fee schedule of fiscal year 2012.

4.5. Statistical analysis

With regard to the treatment effectiveness of the three drugs, the difference in the level of decrease in HbA_{1c} over 12 weeks was tested using one-way analysis of variance, with $p < 0.05$ taken to indicate significance. Statistical analysis was done using SPSS 18.0J (SPSS Japan Inc.).

4.6. Ethical considerations

This study adhered to ethical guidelines for clinical studies and was approved by the medical research ethical review board of Gifu Municipal Hospital and the bioethics committee of Gifu Pharmaceutical University. To protect patients' personal information, data were anonymized in a linkable fashion for analysis. Individual patient information could not be specified, and there was no disadvantage to patients. Findings obtained in this study shall be used for no purpose other than academic presentations or publication in academic journals.

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