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原　著

Medical expenses for cilostazol to treat Alzheimer's disease in Japan

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ABSTRACT

Background: Cilostazol (CL) is an antithrombotic agent that was approved for prescribing under Japan's national health insurance system in 2000. Clinical and experimental studies of CL to treat Alzheimer's disease (AD) have been reported since 2009.

Aims: To use the propensity score method to ascertain whether CL reduced medical expenses among patients with AD in a prefecture of Japan.

Methods: Records of 21,181 patients with AD (6,484 males and 14,697 females) from April 2010 to March 2011 were selected from a claims database of the National Health Insurance and the Long-term Care Insurance systems in a prefecture in Japan. Covariates were patient characteristics, comorbidities, and drugs prescribed for AD, i.e. psychoactive agents, narcotics, anticonvulsants, or cholinesterase inhibitors. The outcome variable was medical expenses for the whole year.

Results: The propensity score indicated that patients receiving CL had medical expenses ￥10.9 higher than those of patients not receiving CL.

Conclusion: According to the propensity score method, CL did not efficiently reduce medical expenses for patients with AD based on claims data.

Key words; Alzheimer's disease, cilostazol, medical cost, propensity score

Background

Alzheimer's disease (AD) is a chronic progressive neurodegenerative disease [1-3] that poses a severe socioeconomic burden [4-6]. Cilostazol (CL) is an antithrombotic agent [7, 8] that has become available under Japan's National Health Insurance system since 2000. CL is reported to prevent pathological changes of AD in experimental animal models [9, 10]. Clinical use of CL to treat AD was first reported in 2009 [11], and subsequent studies have been reported [12-13, 16]. CL was occasionally prescribed to patients with AD for its antithrombotic effect since CL was not approved for prescription to patients with AD at the time. Therefore, one could assume that CL was prescribed to

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patients with AD in a seemingly random manner, representing a "natural experiment" [14]. If CD was clinically effective in treating AD, then it should reduce medical expenses for patients.

A propensity score is the probability that a unit will be assigned to a particular treatment given a set of observed covariates, and it is used to reduce selection bias by equating groups based on covariates.

A search revealed no studies of medical expenses for CL to treat AD. Therefore, the propensity score method was used to analyze medical expenses for CL to treat AD.

Aims

The aim of this study was to use the propensity score method to ascertain whether CL reduced medical expenses among patients with Alzheimer's disease in a prefecture of Japan

Methods

Records of 21,181 patients with AD (6,484 males and 14,697 females) from April 2010 to March 2011 in a prefecture in Japan were selected from a claims database of the National Health Insurance and the Long-term Care Insurance systems (Figure 1). The characteristics of the prefecture were as described in a previous study [15]. Covariates were patient characteristics (age, sex, address), comorbidities, and drugs prescribed for AD, i.e. psychoactive agents, narcotics, anticonvulsants, or cholinesterase inhibitors (Table 1).

The outcome variable was medical expenses (log-transformed) for the whole year (Table 2). The propensity score method was used to compare patients who were prescribed CL and patients who were not prescribed CL. Comparison was performed using the open-source statistical software R (version 3.3.2).

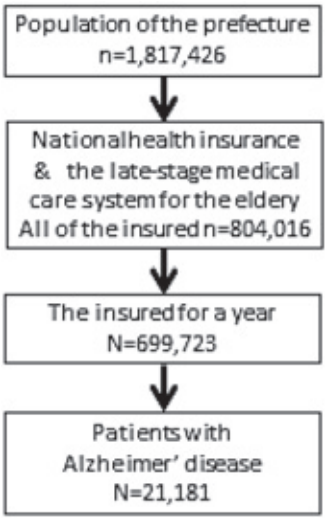

Figure 1. Flow chart of the study

Ethical Considerations

This study was approved by the ethical committee of Kokushikan University (no. 17-003).

Funding

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Conflict of Interests

There were no conflicts of interests in this study.

Results

The profile of both groups of patients is shown in Table 1. Patient characteristics, comorbidities, and prescribed drugs differed markedly. Patients receiving CL had higher medical expenses than patients not receiving CL (Table 1).

The receiver operating characteristic (ROC) curve is shown in Figure 2, and the C-statistic was 0.7484 (95%CI 0.74–0.7569). The distribution of the 2 groups is shown in Figure 3. The distribution indicated that data were amenable for analysis using the propensity score method.

The propensity score indicated that medical expenses for patients receiving CL were ￥10.9 higher than those of patients not receiving CL, and this difference was significant (Table 2).

Discussion

The propensity score indicated that medical expenses for patients receiving CL were only 1 yen higher than those for patients not receiving CL, although this difference was significant. The difference was so small that one could not confidently claim that CL reduced medical expenses for patients with AD.

Experimentally, CL has been tested in mice that received central injections with amyloid beta. Repeated administration of CL reduced the accumulation of amyloid beta and tau phosphorylation [9] and improved cognitive performance in several behavioral paradigms [10].

Table 1. profile of cilostazol (+) group and cilostazol (-) group

Variable		Cilostazol(-) n=17,102	%	Cilostazol(+) n=4,079	%	total n=21,181	%	p-value
attribute	sex (female)	11,925	69.7	1,307	32.0	13,232	62.5	<0.0001
	age 0-64 years	217	1.3	67	1.6	284	1.3	ns
	65-74	1,305	7.6	335	8.2	1,640	7.7	
	75-84	7,950	46.5	1,881	46.1	9,831	46.4	
	85-	7,630	44.6	1,796	44.0	9,426	44.5	
	urban region (city)	11,530	67.4	2,872	70.4	14,402	68.0	<0.0001
comorbidity	hypertension	10,356	60.6	2,523	61.9	12,879	60.8	ns
	diabetes mellitus	4,957	29.0	1,227	30.1	6,184	29.2	ns
	endocrine disease (excl.DM)	151	0.9	55	1.3	206	1.0	ns
	ischemic heart disease	3,976	23.2	1,054	25.8	5,030	23.7	0.0005
	cerebrovascular disease	7,543	44.1	2,118	51.9	9,661	45.6	<0.0001
	malignant neoplasm	2,741	16.0	747	18.3	3,488	16.5	0.0004
	renal disease	1,684	9.8	512	12.6	2,196	10.4	<0.0001
	Admission	4,875	28.5	2,006	49.2	6,881	32.5	<0.0001
prescribed agent	Anxiolytic agent	2,326	13.6	1,239	30.4	3,565	16.8	<0.0001
	Antidepressant	1,263	7.4	909	22.3	2,172	10.3	<0.0001
	Hypnotic agent	2,911	17.0	1,894	46.4	4,805	22.7	<0.0001
	Anticonvulsant	498	2.9	499	12.2	997	4.7	<0.0001
	choline-esterase inhibitor	11941	69.8	3218	78.9	15159	71.6	<0.0001
	narcotics	117	0.7	38	0.9	155	0.7	ns
outcome	medical cost , quantile, ¥	1st 2nd 3rd	78,680 225,600 443,200	1st 2nd 3rd	162,800 352,900 602,800	1st 2nd 3rd	87,430 251,100 473,000	<0.0001

Table 2. results of propensity score method

	estimate	std. error	t-value	p-value
medical cost ¥	10.9	10.2	3.84	0.0001

In 2009, Arai et al. first reported administering 100 mg of CL per day as an add-on to donepezil to 10 patients with mild to moderate AD [11]. A subsequent study examined the effect of CL on cognition and regional cerebral blood flow in elderly patients with AD and cerebrovascular disease over a period of 6 months [16], but patients receiving CL exhibited no change in cognitive function as reflected in their test scores, whereas the control group exhibited a cognitive decline on the Alzheimer's Disease Assessment Scale-Cognitive subscale. When healthy subjects were acutely

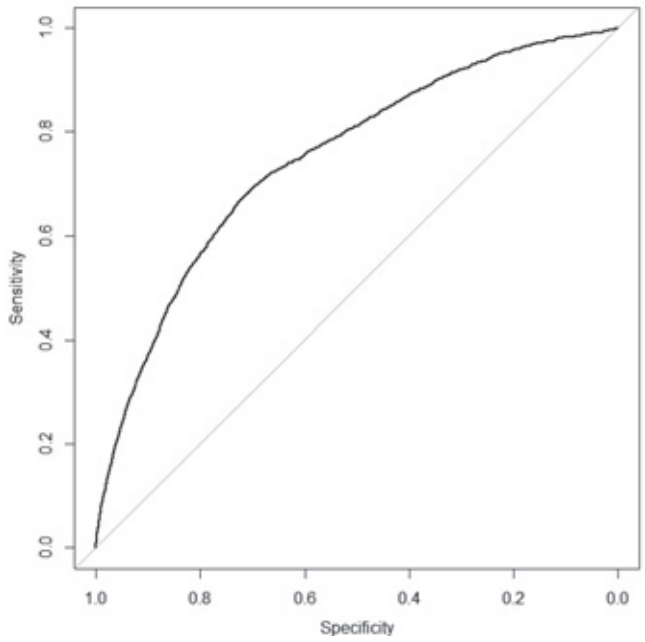

Figure 2. ROC and c-statistics

ROC curve showed adequate separation of two groups as C-statistics was 0.7484 95% CI 0.7400-0.7569). The C-statistics was acceptable for the propensity score method.

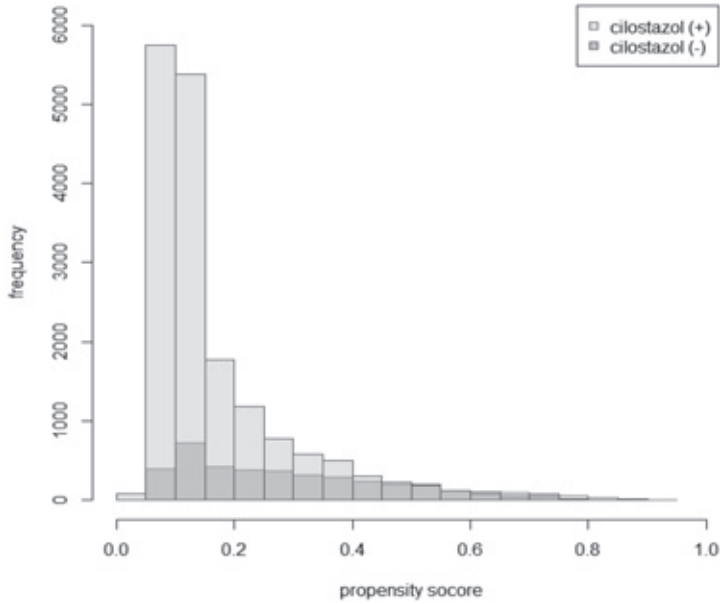

Figure 3. distribution of propensity score

The two groups had clearly different shapes.

treated, an increase in cerebral blood flow was not noted. A later study compared the effects of CL and donepezil and donepezil alone on subcortical white matter hyperintensities in patients with mild to moderate AD. Patients receiving CL and donepezil or donepezil alone did not differ in cognitive measures, which included the Mini-Mental State Examination (MMSE) and the Cognitive subscale of the Alzheimer's Disease Assessment Scale. A recent case-control study examined 60 patients with stable AD receiving acetylcholinesterase inhibitors; patients were equally divided into a placebo group and a group receiving CL as an add-on therapy for at least 12 months. CL was found to improve the MMSE score and the Clinical Dementia Rating sum of boxes scores of patients with AD already receiving acetylcholinesterase inhibitors [17].

In addition, two retrospective studies reported that average doses of CL for 6 months alleviated mild cognitive impairment according to the MMSE score [18, 19]. These clinical studies seem to indicate that CL might improve cognition, and particularly in patients with mild cognitive impairment and mild AD [13]. A randomized control trial of CL in treating mild cognitive impairment is reported to be underway [20].

An economic evaluation of using CL to treat AD is needed to reduce the economic burden of care for AD [1, 2].

Limitations

The current study had several limitations. The first is that this study was an observational study and not a randomized control trial.

The second limitation is that data on claims in one prefecture were selected from a database of the National Health Insurance and the Long-term Care Insurance systems. The prefecture had an average profile among the 47 prefectures in Japan [15]. Presumably, the current results could be generalized to Japan as a whole.

The third limitation is that psychoactive agents and narcotics served as covariates to control for confounders. However, the propensity score method is not able to control for unmeasured confounders. Thus, uncontrolled confounders may exist.

Conclusion

According to the propensity score method, CL did not efficiently reduce medical expenses for patients with AD based on claims data.

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