Results

Table 1 shows symptom-free and exacerbation rates of the standard therapy group and rate ratios for the omalizumab add-on group and responder subgroup relative to the standard therapy group. Confidence intervals of the rate ratio under log-normal distribution were used as the range for probabilistic sensitivity analysis. Utility values and asthma-related mortality risks were shared among the two groups and the responder subgroup (Table 1). Omalizumab cost, standard therapy cost, and unit cost of health care resource use are also provided in Table 1.

The results of the base-case analysis with the primary utility set are presented in Table 2. The mean lifetime discounted costs and QALYs were $43,000 and 16.00, respectively, for the standard therapy group and $114,100 and 16.10, respectively, for the omalizumab add-on group. The results produced an ICER of $755,200 per QALY, with the 95% CI ranging from $614,200 to $1,298,500 for the base-case analysis of the omalizumab add-on group relative to the standard therapy group.

In the base-case analysis with the alternative utility set, the ICER was $633,500 (95% CI $515,300–$1,054,500) per QALY gained (Table 2).

Sensitivity Analysis

A tornado diagram of one-way sensitivity analyses with the primary utility set is shown in Fig. 2. The results indicate that the ICER was sensitive to the risk of death from hospitalization ($550,700–$1,225,200), rate ratio for hospitalization ($678,500–$1,143,400), utility for symptom-free asthma ($625,500–$1,042,200), rate ratio for symptom-free asthma ($654,400–$878,400), discount rate ($612,700–$826,500), utility for day-to-day asthma ($675,700–$855,900), and omalizumab cost ($679,400–$755,200). The ICER decreased by 10% when the omalizumab cost was reduced by 10%. Threshold analysis identified a break-even price of $40 for a 150-mg vial of omalizumab. In the subgroup analysis of patients with particularly severe asthma, the ICER was $583,600 (95% CI $462,300–$1,308,900) per QALY gained.

The cost-effectiveness acceptability curve illustrates the cost-effectiveness probability of omalizumab over a range of willingness-to-pay (WTP) values (Fig. 3). For a WTP threshold value of $728,000, the cost-effectiveness probability of omalizumab was 51%.

EVPI for Response to Omalizumab

In the responder subgroup analysis with the primary utility set, the mean lifetime discounted costs and QALYs were $155,300 and 16.19, respectively, resulting in an ICER of $590,100 (95% CI $430,700–$858,600) relative to the standard therapy group (Table 2). The ICER (point estimate) for the responder subgroup was 22% lower than that for the omalizumab add-on group (i.e., the base-case analysis).

In the value of information analysis with the primary utility set, the individual EVPI was $4100 (95% CI $2500–$6000) at a threshold value of $45,000 per QALY. The population EVPI for total eligible patients with severe asthma (7200 patients) amounted to $28 million (95% CI $17 million–$42 million) per year.

Discussion

In the present study, we analyzed the cost-effectiveness of omalizumab add-on therapy relative to standard therapy alone, on the basis of clinical data from an RCT carried out in Japan. The

Table 2 – Lifetime outcomes and costs in economic evaluation of omalizumab.

	Analyses with the primary utility set			Analyses with the alternative utility set		
	Standard therapy group	Omalizumab add-on group* (95% CI)	Responder subgroup† (95% CI)	Standard therapy group	Omalizumab add-on group* (95% CI)	Responder subgroup† (95% CI)
Outcome						
Life years, undiscounted	33.96	34.04 (33.95–34.07)	34.09 (34.07–34.11)	33.96	34.04 (33.95–34.07)	34.09 (34.07–34.11)
QALYs, undiscounted	26.38	26.51 (26.42–26.54)	26.63 (26.56–26.70)	27.96	28.11 (28.03–28.14)	28.25 (28.17–28.33)
Life years, discounted	20.60	20.65 (20.59–20.66)	20.68 (20.66–20.69)	20.60	20.65 (20.59–20.66)	20.68 (20.66–20.69)
QALYs, discounted	16.00	16.10 (16.05–16.12)	16.19 (16.14–16.26)	16.96	17.07 (17.02–17.10)	17.19 (17.12–17.26)
Cost ($, discounted)						
Total costs	43,000	114,100 (114,000–114,200)	155,300 (155,300–155,300)	43,000	114,100 (114,000–114,200)	155,300 (155,300–155,300)
ICER (vs. baseline, discounted)						
Cost per QALY ($/QALY)	Baseline	755,200 (614,200–1,298,500)	590,100 (430,700–858,600)	Baseline	633,500 (515,300–1,054,500)	491,900 (364,100–687,400)

CI, credible interval; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.
* Omalizumab add-on group indicates the total number of patients treated with omalizumab plus standard therapy.
† Responder subgroup indicates a subgroup of patients who derive great benefits from omalizumab plus standard therapy.

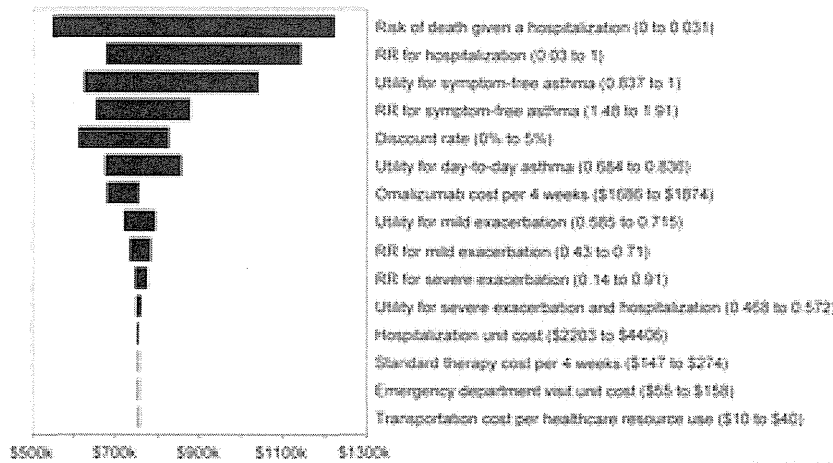

Fig. 2 – Tornado diagram summarizing one-way sensitivity analyses of the incremental cost-effectiveness ratio (cost per quality-adjusted life-year) of omalizumab plus standard therapy relative to standard therapy alone. RR indicates rate ratio for omalizumab plus standard therapy relative to standard therapy alone.

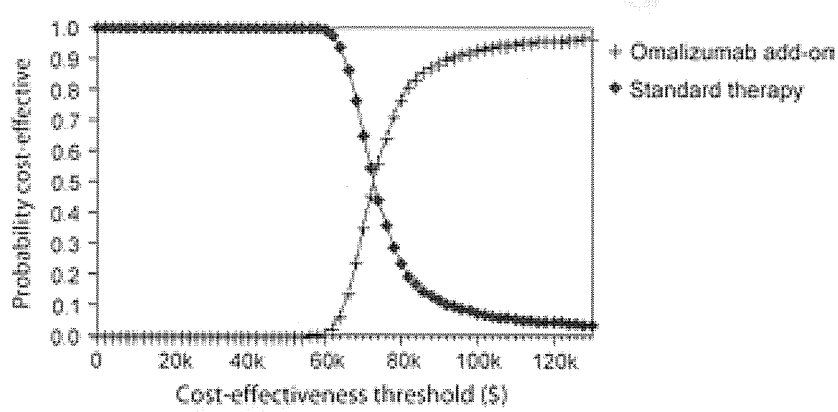

Fig. 3 – Cost-effectiveness acceptability curve. This graph illustrates the probability that a treatment strategy is cost-effective over a range of willingness-to-pay thresholds for an additional quality-adjusted life-year.

results showed that omalizumab was not cost-effective given the existing evidence.

We demonstrated that the ICER was sensitive to omalizumab cost and that the cost-effectiveness was improved when omalizumab add-on therapy was targeted at responders or patients with particularly severe asthma. The best ways to improve the cost-effectiveness of omalizumab may include decreasing the price of omalizumab, restricting omalizumab therapy to a subgroup of patients with a higher risk of exacerbation, which has been recommended by the National Institute for Health and Clinical Excellence [12], and confining the intervention to previously predicted responders identified on the basis of pretreatment patient characteristics. Further research should be performed on omalizumab response prediction methods (e.g., genetic testing) to help physicians decide whether to begin omalizumab add-on therapy. The development of prediction methods for patients' response to omalizumab will considerably improve the ICER. We calculated the EVPI for omalizumab response to estimate the value of further research for developing prediction methods, although the estimation of EVPI is uncommon in economic evaluations in which the ICER is far from the WTP threshold. Thus, caution is required to assess the quantitative results, and further studies should involve real testing value for responders. However, our findings suggest the importance of prediction methods.

Dewilde et al. [7] and Brown et al. [8] demonstrated that omalizumab therapy was cost-effective in patients with severe asthma. In contrast, Campbell et al. [9] presented an ICER of $287,200 and $172,300 per QALY gained in the base-case analysis and the responder scenario analysis (where nonresponders remained and received 16-week omalizumab therapy), respectively. Wu et al. [10] analyzed the relationship between HRQOL and lung function parameters and concluded that omalizumab, with an ICER of $821,000 per QALY gained, was not cost-effective. One possible explanation for the inconsistency between the results from the former three studies using Markov models and the present study may be the difference in model structure. Our model included the symptom-free state to distinguish nonexacerbation utilities of the omalizumab add-on group from those of the standard therapy group. Furthermore, there is a difference in how asthma-related death is linked with other states in the models. Campbell et al. [9], as in our study, linked asthma-related death with the hospitalization state, whereas Dewilde et al. [7] and Brown et al. [8] assumed that patients transitioned from the severe exacerbation state to asthma-related death at a 2.082% to 3.108% risk in their model, which did not include the hospitalization state. Considering that severe exacerbations were more frequent than hospitalizations, more patients should have died from asthma in the models of Dewilde et al. and Brown et al.,

compared with our model and that of Campbell et al., thus creating a bias in favor of omalizumab. Another explanation is the difference in the price of a 150-mg vial of omalizumab.

Strengths and Limitations

Our study has several advantages compared with those reported in the literature. To the best of our knowledge, the present study is the first to explore the efficient use of omalizumab and assess the value of further research to eliminate the uncertainty associated with patients' response to omalizumab. Another advantage is the first economic evaluation using clinical and cost outcomes of omalizumab from an Asian population. In Japan, medical fees for health care services are relatively low among Organisation for Economic Co-operation and Development countries [15]. Chronic diseases, such as asthma, that involve the repeated use of urgent health care services underscore the importance of conducting the economic evaluation of an expensive drug in the Japanese setting.

Our analysis also has assumptions and limitations. First, the input data for HRQOL utilities were derived from another study conducted outside Japan. The generalizability of HRQOL in asthmatic patients to other countries might be limited [18]. Considering this limitation, we presented the omalizumab-favorable scenario in which the alternative utility set had a broader utility range than that in previous studies, as recommended in the practical guide for economic evaluations that involve parameter uncertainties [29]. This means that our alternative utility set was the most favorable to omalizumab. Yet, omalizumab was not cost-effective. These ensure that our findings are rigorous. Second, our value of information analysis was based on structural uncertainties. Experts have been advocating how to handle this type of uncertainty [30]. There are, however, limited examples of working on this issue in economic evaluations of health interventions. Third, clinical data of the response to omalizumab were not available from the RCT in Japan. We advocate that data of responders should be collected alongside further clinical trials. Finally, we extracted clinical parameters of the overall patients treated with omalizumab and omalizumab responders from different clinical trials to estimate the EVPI for omalizumab response. Further research exploring EVPI more precisely by using clinical data from a single trial may be needed.

Conclusions

We conclude that omalizumab is not cost-effective in Japan given a WTP of $45,000 per QALY. Omalizumab, however, will remain in the market because it possesses a unique mechanism of action and provides great benefits to patients with severe asthma, particularly responders. The cost-effectiveness of omalizumab may be improved if omalizumab therapy could be confined to previously predicted responders. Future studies to investigate prediction methods for the identification of responders are of great value. Caution, however, is required in interpreting the EVPI for omalizumab response, given the assumptions and the structural uncertainties. We look forward to a reduction in the price of omalizumab, which will improve cost-effectiveness.

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Improving the assessment of prescribing: use of a 'substitution index'

Abstract

OBJECTIVE: To analyze current and potential utilization of generic drugs in Japan, to examine maximum possible cost savings from generic drug use, and to develop a fairer measure to assess the level of generic drug substitution.

METHODS: We conducted a cross-sectional retrospective analysis of nine million dispensing records during January to March 2010 in Kyoto Prefecture. Maximum potential quantity-based shares were defined as the quantity of generic drugs used plus the quantity of branded drugs that could have been replaced by generic drugs divided by the quantity of all drugs dispensed. We developed a "substitution index," defined as the proportion of generic drugs out of the total drugs substitutable with generic drugs (based on quantity rather than cost).

RESULTS: Generic drugs had a quantity-based share of 17.9%, a cost-based share of 8.9%, and a maximum potential quantity-based share of 50.1% which is lower than the actual generic drug shares of some other countries. The maximum possible cost savings as a result of generic drug substitution was 16.5%. We also observed wide variations in maximum potential quantity-based shares between health care sectors and health care

institutions.

CONCLUSIONS: Simple comparisons based on quantity-based shares may misrepresent actual generic drug use. A substitution index that takes into account the maximum potential quantity-based share of generic drugs as a fairer measure, which may promote more realistic goals and encourage generic drug usage.

Introduction

In response to a global trend of rising health care costs, the increased use of generic drugs is one mechanism to reduce financial burdens on patients, payers and health care systems. (1-4) However, Japan has reported lower generic drug utilization compared to Europe and the US.(5) Total health care costs in Japan in 2009 were approximately 36 trillion yen (USD 323 billion) and drug costs in 2010 made up 24% at 8.7 trillion yen (USD 78 billion). (6) In 2007, the Japanese Cabinet Office's Council on Economic and Fiscal Policy set a target for the quantity-based share of generic drugs (the proportion of drugs prescribed that are generic, as regards the quantity of drugs) to double to 30% by 2012. (7)

To achieve this, financial incentives were implemented. Until March 2010, community pharmacies had been awarded an additional payment if the proportion of generic drugs dispensed was over a stipulated proportion. In contrast, hospitals decide in advance what drugs to provide for inpatients. Therefore, the choice between generic and branded drugs is made at the organizational level and is beyond the influence of individual pharmacists. However, a pharmacist dispensing for outpatients may substitute generic drugs for branded drugs unless a doctor stipulated no substitution. The maximum potential generic drug use at both national and institutional levels has yet to

be determined. Depending on hospital type and clinical specialty, the maximum proportion of generic drugs that could be used by a provider may be drastically different to other providers. Therefore, decisions to award or withhold financial incentives to individual institutions based on common targets are inherently unfair.

Although the approximate cost savings from generic drugs has been suggested by the government, (8) accurate estimates need to be based on unit costs and utilization.(9) Computerization of claims to medical insurance systems means that a comprehensive database is available for such estimates to be made.

Our objectives were to examine recent generic drug use in Japan, to reveal the maximum potential use of generic drugs, to simulate possible cost reduction from generic drug use within different health care sectors, and to develop a fair assessment measure of generic drug use. This study is limited to prescription drugs and does not include those bought over-the-counter.

Methods

Data source

We used a cross-sectional analysis of dispensing records from insurance claims submitted to the National Health Insurance (NHI) and Long Life Medical Care (10) systems between January and March 2010 by health care providers in Kyoto Prefecture.

This database includes 9,111,618 dispensing records from 169 inpatient facilities, 1105 outpatient facilities, and 747 community pharmacies. Japanese hospitals are reimbursed using either a fee-for-service or flat-sum system. The latter refers to the Diagnosis Procedure Combination/Per-Diem Payment System (DPC/PDPS), which was introduced in 2003. Providers are required to report the actual utilization of each item, which we used to calculate the amount of drug use.

Analyses were conducted for three health care sectors: outpatients in clinics and hospitals; inpatients; and community pharmacies. Institutions which dispensed fewer than 100 units per month were excluded.

Quantity and cost of drugs

We calculated the usage of all drugs, both generic and branded, and the cost according to the Japanese NHI Drug Price Standard list in use in 2010. Costs were calculated in Japanese yen and converted to US dollars using the purchasing power parity rate in 2010 (JPY111.39= USD1).

Identification of branded and generic drugs and substitutability for generic drugs

Branded and generic drugs were priced according to the NHI Drug Price Standard list. Generic drug substitutability was determined using the drug codes provided on that list. Each drug has a unique 12-digit code, which has a categorization function: the first two

digits designate each drug's therapeutic purpose, and the following seven digits indicate its chemical composition, formulation, and dosage. (11,12) The final three digits indicate the brand of each drug. Branded drugs and their corresponding generic alternatives were matched using the first nine digits. The list included 19,355 drugs that could be categorized as: branded drugs with no generic equivalent (n = 9,304); branded drugs substitutable with generic drugs (n = 1,782); and generic drugs (n = 8,269). Simulation analysis was conducted using the 1,782 branded drugs substitutable with generic drugs. Quantity-based share was defined as the proportion of the quantity of all drugs presented that were generic and cost-based share was the same but according to the cost of drugs.

Measures of drug use

Maximum potential quantity-based share was calculated as:

$$\frac{\textit{Maximum quantity of substitutable branded drugs and generic drugs}}{\textit{Quantity of all drugs}}$$

We also conducted a simulation analysis of possible drug cost reduction as a result of maximum generic drug substitution. For branded drugs with multiple equivalent substitutable generic drugs at different prices, we used the mean prices of the generic

drugs to reflect possible cost reduction. The lowest and highest prices were used to provide a sensitivity analysis.

To demonstrate the degree of generic drug usage, we created a substitution index, which ranged from 0 to 1 and was defined as:

$$\frac{\textit{Quantity of generic drugs}}{\textit{Quantity of generic drugs} + \textit{Quantity of substitutable branded drugs}}$$

This can also be expressed as:

$$\frac{\textit{Quantity-based share}}{\textit{Maximum potential quantity-based share}}$$

Results

The proportion of generic drugs based on quantity (17.9%) and cost (8.1%) are shown in Table 1 together with the maximum potential proportion (based on quantity)(10.1%). Figure 1 shows the quantities and utilization rates of branded drugs with no generic equivalent, substitutable drugs, and generic drug use across all therapeutic categories as defined by the Japanese Ministry of Internal Affairs and Communications. (12) The quantities and substitutability of drugs dispensed differed widely between therapeutic

categories. Cardiovascular medications, including antihypertensive and antihyperlipidemic agents, were the second largest in quantity dispensed and had the largest potential quantity for substitutability with generic drugs.

Possible cost reduction as a result of generic drug substitution for outpatients, inpatients, and pharmacies was estimated to be 15.4% inter price-dependent range: 12.1%–17.5%), 9.4% (8.0%–10.2%) and 19.6% (15.3%–22.5%) respectively. Total drug cost reduction was estimated to be 16.5% (13.0%–18.8%) under maximum substitution conditions, equivalent to USD 37 million.

Table 2 shows the maximum potential and the quantity-based shares of generic drugs in health care institutions according to sector. Values differ widely across health care institutions, with some institutions using generic drugs at near-maximum potential whereas others made only limited use. Several institutions showed a very low maximum potential quantity-based share; the lowest among the pharmacies was 1.2%.

Figure 2 shows the quantity-based share generic drug use and the substitution index of each health care institution. There were wide variations in substitution index among institutions that scored near the quantity-based share; 40% (75 out of 187) that were in the lowest quartile according to their quantity-based share were in the top two quartiles according to their substitution index.

Discussion

Main findings

Generic drug quantity-based share was 17.9%, similar to that reported by the Japanese government. (13) The maximum potential quantity-based share of generic drugs was 50.1% suggesting generic drugs are used in only 36% (17.9% out of 50.1%) of potential opportunities. In addition, the maximum potential quantity-based share in Japan is lower than the generic drug quantity-based shares in the UK (53%) and the US (55%).(5) This might be explained by the rapid diffusion of new drugs in Japan(4) which means that the number and quantity of new drugs that are not substitutable with generic drugs is high. Although the Japanese government has constructed macroeconomic policies that take these figures into account, (5) simple comparisons or target setting may be irrelevant. In other words, assessments based on quantity-based shares may misrepresent the situation.

Implications

The different maximum potential quantity-based shares across institutions are likely due to differences in proportions of the types of drugs that are dispensed in each institution rather than on differential efforts of institutions to use generic drugs. As

Japanese pharmacies currently receive financial incentives based on their quantity-based shares, these results suggest that the current incentives use an intrinsically unfair goal.

The substitution index proposed assesses the use of generic drugs in the context of substitutability, thereby reflecting their maximum potential quantity-based share. Institutions with similar quantity-based shares can score very differently when using the substitution index, and vice versa. Therefore, evaluations by the quantity-based share may undervalue individual institution efforts, as well as present a relatively weak incentive as some institutions can achieve high values without much effort if they have a high maximum potential. In contrast, institutions with low potential substitutability may not find it advantageous or even possible to increase the quantity of generic drugs dispensed in order to benefit from financial incentives. The substitution index may represent a fairer and feasible alternative to the present incentive-linked measurement to encourage generic drug use. The results of future analyses may change if doctors change prescriptions from unsubstitutable drugs to those substitutable for generic drugs, or if generic drugs become available for currently unsubstitutable ones. However, the index proposed here can still be applied, with modifications to the denominator, to reflect any drug switching.

An important contribution of this study is the analysis at the individual sector

and health care institution levels. Previous reports have been mainly based on aggregated data, and arguments and incentives have therefore been geared toward aggregated data scores. However, the recent shift to electronic databases for health care claims data in Japan has allowed more detailed analyses and enables the development of better indices for monitoring drug utilization and related costs; fairer criteria can also be determined for the evaluation of future incentives aimed at encouraging generic drug use. Not only must new incentives be considered carefully before implementation but current incentives must be evaluated for potential replacement. (14-16) As concerns remain about the efficacy of generic drugs, (17-20) this study does not address how large the share of generic drug utilization should be. Instead, we propose a fairer indicator to monitor generic drug use at the health care institution level.

Limitations

Our results should be interpreted with some caution due to potential bias from the data source. First, the data covered only three months so did not take into account seasonal variation in use. Second, the data were based on a single prefecture though generic drug use has been shown to be similar across prefectures.(13) The insurers providing the data cover more than 70% of all public insurance benefits.(21) A national database, which the Japanese government is currently developing, may allow analyses

of all prefectures in the future. Another possible limitation is that drug prices are regulated by the government and cost-shares may change over time even if quantity-shares remain unchanged.

Conclusions

Generic drug usage in Japan remains low despite government efforts. Simple comparisons based on quantity-based shares may misrepresent generic drug use. Wide variations in maximum potential quantity-based shares between health care sectors and health care institutions due to differences in substitutability suggest that a substitution index, that takes into account the maximum potential quantity-based share, is a fairer assessment measure that can promote more realistic goals and more effectively encourage generic drug usage.

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