投稿論文

An Analysis of Pharmacoeconomic Studies in Japan

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We collected original published pharmacoeconomic studies conducted in Japan, through systematic database retrieval and other methods. Criteria for reviewing the studies were developed through an analysis of papers, textbooks, and regulatory guidelines in Australia, Canada, the U.K., and the U.S. The 10 Japan-based pharmacoeconomic studies were reviewed according to these criteria. A previous quality review of economic analyses in health care conducted in the U.S. was used as a reference for comparison. The overall quality of the Japan-based papers showed similar problems to the sample of U.S. papers on one criterion and ranked higher on two criteria. The analysis identified areas for improvement of Japan-based pharmacoeconomic studies, since most of the Japanese papers lacked some important elements of economic evaluation, such as clarification of viewpoints and sensitivity analysis on the discount rate.

Key words: pharmacoeconomics, review, cost-effectiveness analysis

[Introduction]

Pharmacoeconomic (PE) research identifies, measures and compares the costs (resources consumed) and consequences/outcomes (monetary benefits, effectiveness, quality of life, utility, efficacy, safety, morbidity, mortality) of pharmaceutical products[1]. One example is a comparison of the cost-effectiveness of a new drug therapy to that of a standard existing therapy. Most PE studies provide integrated information about the costs and effects of pharmaceuticals in the form of ratios, for example, using cost-effectiveness.

In the United States, Canada, some European countries, and Australia, this field has become well established. In some countries, like Australia and Canada, it has become an important tool for health policy making.

Although the field of pharmacoeconomics is still developing in Japan, and is almost never applied in health policy making, the economic aspect of pharmaceuticals is a major issue of health care financing in Japan. One reason is that Japan consumes more than 20% of all the pharmaceuticals in the world (by value), and approximately 30% of Japan's health care expenditure is spent on pharmaceutical reimbursement. The high price of drugs in Japan, as well as the total volume of drug consumption, contribute to this phenomenon. PE studies could also play an important role in health policy making in Japan, because under the national health insurance system, the government decides the prices of pharmaceuticals. Under these circumstances, it is appropriate for Japan to consider the feasibility and usefulness of PE studies in health policy making.

This study assesses the state of development of PE studies in Japan through a review of published studies of economic evaluation on pharmaceuticals and discusses the existing problems and future possibilities of PE studies in Japan.

[Methods]

Previous quality review studies of economic evaluation in health care have examined whether the important components of cost-effectiveness studies were included in the analyses[2,3]. This study aimed to undertake a similar quality review for Japanese PE studies. However, widely accepted quality review criteria are not currently available. Hence we first developed our own quality review criteria, and then applied the criteria to a sample of published PE studies.

The criteria for the review of the Japanese PE studies

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were developed by comparing the existing guidelines on PE studies (both mandatory and voluntary) for Australia, Canada, the U.S., and the U.K. with two well-known papers in the academic literature[2,3] to identify commonalties.

The available published papers of PE analyses conducted in Japan were collected through a systematic analysis of 4 major medical databases in Japan and the United States (Igaku-Chuo-Zasshi, JMEDICINE, MEDLINE, and HEALTH) and through non-database methods. Only those studies fulfilling the following criteria were selected using a two-stage process. We first selected studies from the searches on the basis of title, key words and abstracts, and then in the second stage, we read the original articles for those selected in the first stage to assure that each study met three criteria:

1) The articles must focus on a comparison between costs and effectiveness/benefits of therapies (including cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA)), and at least one of the alternatives must be a human drug therapy. Human drugs here include those regarded as pharmaceuticals in Japan, such as diagnostic agents and vaccines, as well as other drugs.
2) The study must be a published paper, and not a proceedings, review article, editorial, or letter.
3) The study must be Japan-based.

[Results]

Collection of Articles for Review

The terms used to retrieve studies from the four medical databases and the results achieved are described below. The database retrieval identified 9 articles that met the criteria as Japan-based PE studies for evaluation.

(1) IGAKU CHUO ZASSHI ("Medical Central Magazines") : 1 study

Terms used: "Hiyo" (meaning "Cost"), "Hiyo Koka" (meaning "Cost-Effectiveness") or "Hiyo Koka Bunseki" (meaning "Cost-Effectiveness Analysis"). Papers were retrieved that were entered into the database between 1988 and 1994 (since papers during this time period were easily retrieved with the search system in use). We retrieved 107 articles. Only 5 articles out of the 107 were on pharmaceuticals, and 3 articles out of the 5 retrieved were proceedings. This left 2 articles. Out of the 2 articles on pharmaceuticals, only one was an economic analysis using actual data (the other presented a methodology for economic evaluation of antihypertensive drugs).

(2) JMEDICINE: 5 studies

Terms used: "Hiyo Koka Bunseki" (meaning "Cost-Effectiveness Analysis"), "Hiyo"&"Koka" (meaning "Cost" & "Effectiveness"), "Hiyo Koka" (meaning "Cost - Effectiveness"), "Hiyo"&"Ben - eki" (meaning "Cost"&"Benefit"), "Hiyo Ben-eki" ("Cost-Benefit"), "Cost" & "Effectiveness", "Cost" & "Benefit". The search was narrowed down by "Kusuri" (meaning drugs, pharmaceuticals or medicines) or "Yakuzai" with a meaning similar to "Kusuri") or "Yakubutsu" (with a meaning similar to "Kusuri"). 112 articles were retrieved from the database (after 1981). Based on the title and abstract search, 4 articles were not Japan-based studies. Of the remaining 108 articles, 99 articles included something on human drugs (excluding insecticides, veterinary drugs, diagnostic agents, disinfectants, trials on tissues or animals, etc.) Of these, 30 articles were focused on the clinical evaluation of pharmaceuticals. Of these 30 articles, 11 articles had the words "Hiyo Koka (Bunseki)", "Hiyo Ben-eki (Bunseki)", "Cost-Effectiveness", "Cost-Benefit" in the title or key words section.

For these 11 articles, we read each original article to determine whether the study was appropriate for evaluation. 6 articles qualified as Japan-based PE studies (such as CMA, CEA, CUA, CBA). One study overlapped with the article retrieved from the search of IGAKU CHUO ZASSHI, leaving 5 studies.

(3) MEDLINE: 1 study

Terms used: "Cost-benefit analysis" or "Cost and cost analysis" (both were the medical subject headings) and these were narrowed down by "Japan". The search was conducted for papers entered into MEDLINE between 1990 and 1994. 26 articles (all written in English) were retrieved. Out of these, 22 were Japan-based studies, and 13 included cost analysis or cost-effectiveness analysis. Out of these 13 articles, only 1 was an analysis of pharmaceuticals.

(4) HEALTH: 2 studies

Terms used: "Cost-benefit analysis" or "Cost and cost analysis" (both were the medical subject headings) and these were narrowed down by "Japan." We searched all papers in the Health database (the oldest retrieved was from 1978). 54 articles were retrieved. All but 2 articles were either not Japan based or did not include cost analysis of pharmaceuticals.

(5) Non-database Retrieval: Since the database retrieval identified only 9 relevant articles, we also looked for other articles by interviewing several researchers versed in this field. As a result, we added 1 other Japan-based PE study.

Profile of Retrieved Japanese PE Studies

The sample of 10 studies collected in the retrieval process was classified according to the year of publication, as shown in **Table 1**[4-13].

The trend of development for economic analyses in health care has been examined for U.S. studies by Elixhauser et al [14]. They classified the retrieved articles by publication type (reports of study or other), topic areas (250 different topic areas), study type (CBA or CEA), medical function (preventive, diagnostic, therapeutic), publication vehicle (medical journal or non medical journal), and then analyzed changes in number. Our sample of Japan-based PE studies, however, is too small for reliable trend analysis of this kind. A second characteristic of our sample is the small number of studies retrieved. The small number may reflect problems in the system of database retrieval (as suggested by the additional article identified through the non-database search method), or the reluctance of major medical journals in Japan to publish articles from a relatively undeveloped field such as pharmacoeconomics.

A third notable characteristic of our sample is that 5 out of the 10 studies were performed by the same first author. This pattern shows that, as yet, only limited human resources have been invested in the pharmacoeconomic field in Japan, and that only a small number of experts have been working on such studies.

Comparison of Academic and Regulatory Guidelines

One source for quality review criteria is standards used in excellent academic articles in evaluating articles of economic analysis in medical practice. One well-known guideline was published by Drummond et al [2]. A modified version of this guideline was prepared by Eisenberg[15]. The U.S. Office of Technology Assessment[16] used basic elements that closely resemble these two guidelines. Another source of such guidelines is quality reviews of economic studies of medical practice, such as the study by Udvarhelyi et al. [3] that established minimum standards for economic analysis. These guidelines and the classical literature on economic analysis of medical practices[17-23] contain several criteria that are almost universally observed.

Another source of quality review criteria is regulatory guidelines (both mandatory and voluntary). Australia, Canada, the U.K., and the U.S. have all adopted some form of guidelines on PE studies by the regulatory authority[24-29]. These regulatory guidelines have much in common with the "academic" standards. However, the objectives of regulatory standards and those of academic standards may differ somewhat. For example, the main objectives of academic standards are to evaluate the "quality" and "scientific soundness" of the study, and to assure valid and unbiased results that are relevant to the study's purposes. On the other hand, regulatory standards have additional concerns, such as making the economic analysis results conform to the regulator's own decision-making process. Regulatory guidelines are also concerned with promoting better comparability between studies by recommending a standard methodology, even if it is not necessarily the best method from an academic viewpoint.

Selection of Review Criteria

Our review of academic and regulatory guidelines identified eight important and common elements of the economic analysis of medical practice: the viewpoint of the analysis (perspective, e.g. societal, payer), compar-

Table 1 Pharmacoeconomic Studies Selected for Review

Auocor, Year	Type of study	Disease	Drug names	Journal name
Fujino et al, 1985	CMA	gastric ulcer	cimetidine, teprenon	Health Policy
Sasaki & Eisenberg, 1987	CEA	esophageal varix	unspecified*	Intl J Tech Ass in Health Care
Fujino et al, 1988	CBA	angina	TTS nitroglycerin	Yakuri to Chiryo
Fujino et al, 1989	CEA	hyperlipaemia	pravastatin	Rinsho Iyaku
Baba et al, 1990	CMA	Kawasaki disease	gamma globuldn	Prog Med
Hayashi et al, 1991	CEA	hepatitis B	hepatitis B vaccine	J Infect
Nishicara, 1991	CBA	mumps	mumps vaccine	Niigata Igakukai Zasshi
Fujino et al, 1992	CEA	obesity	magindol	Shinryo to Shinyaku
Fujino et al, 1993	CEA	gastric ulcer	misoprostol	Kiso to Rinsho
Habu et al, 1993	CEA, CUA	symptomatic gallsto	ursodeoxycolic acid	Nippon Shokakibyo Gakkai Zasshi

(abbreviations)
CMA: cost-minimization analysis, CEA: cost-effectiveness analysis,
CUA: cost-utility analysis, CBA: cost-benefit analysis
*: endoscopic injection sclerotherapy

Table 2 Comparison of Major Items/Requirements Observed in Guidelines or Standards for Economic Analysis

		Regulatory Standards/Guidelines				Academic Standards	
		Canada	Australia	U.K.	U.S.	Udvarhelyi et al.	Drummond et al.
〈1〉 Viewpoint of the analysis (perspective)〉							
1	should be stated	✓	✓		✓	✓	✓
*2	particular perspective recommended (e.g. societal)	✓	✓	✓			
〈2〉 Comparators〉							
1	important comparator(s) should be included						✓
*2	justification of the choice of comparators	✓	✓	✓			
*3	recommendation about appropriate technique	✓	✓		✓		
〈3〉 Type of analysis〉							
*1	justification for the analysis technique selected	✓	✓	✓			
*2	recommendation about appropriate technique	✓	✓				
〈4〉 Costs〉							
1	all relevast costs to the anlysis objective included	✓	✓	✓		✓	✓
*2	recommendation about "relevant costs" to be included	✓	✓	✓			
3	natural physical unit should be measured credibly	✓		✓	✓		✓
4	monetary value of the units should be credibly valued	✓		✓	✓		✓
*5	use of "standard costs" recommended	✓	✓				
〈5〉 Outcomes〉							
1	all relevant outcomes to the analysis objective included	✓	✓		✓	✓	✓
*2	effectiveness not efficacy should be captured	✓					
*3	detailed methods for HRQOL measures required if used	✓	✓		✓		
*4	recommendation/requirements about HRQOL measures	✓		✓			
*5	dctailed methods of measuring QALY required		✓				
*6	recommendation about method for measuring QALY	✓					
*7	racommendation on method of measuring benefitin CBA	✓					
*8	should make sure equity is maintained	✓		✓			
9	Effectiveness should be proven/ established	✓	✓	✓	✓	✓	✓
10	recommended/required data sources for outcomes	✓	✓	✓	✓		✓
〈6〉 Discounting〉							
1	discounting for the future costs if necessary	✓	✓	✓		✓	✓
2	discounting for the future outcomes if necessary	✓	✓	✓		✓	✓
3	justification of the discount rate required				✓		✓
*4	recommendation about the discount rate to be used	✓	✓	✓			
〈7〉 Sensitivity analysis〉							
1	SA for the range of values for key parameters	✓	✓	✓	✓	✓	✓
2	justification for the range of values used in SA						✓
*3	recommendation for the range of values used in SA	✓	✓	✓			
〈8〉 Reporting/summary of the analysis results〉							
1	summary ratios (e.g. C/E ratio)	✓	✓			✓	✓
2	incremental ratio when relevant	✓	✓	✓		✓	✓

(Abbreviations)

HRQOL: health-related quality of life, QALY: quality-abjusted life year, CBA: cost-benefit analysis, SA: sensitivity analysis, C/E ratio: cost-effectiveness ratio

* : Items specific to the regultory standards/guidelines

ator (alternatives), type of analysis, costs, outcomes, discounting for different timings, sensitivity analysis for uncertainty, and reporting of the results. A comparison of the major elements observed in the regulatory and the academic standards for economic analysis is presented in **Table 2**. Most of the items that are included in the academic standards are also included in the regulatory standards (particularly in the Canadian and Australian guidelines).

Overall, those items included only in the regulatory standards and not in the academic standards are mostly prescriptive items or normative items. Several examples are: a particular viewpoint (e.g., societal) is recommended as the perspective of studies; a recommendation is provided about the method of comparator selection (e.g., the most widely used drugs); a recommendation is provided on the costs to be included or excluded; "standard costs" are encouraged to be used in the analysis; and so on.

This comparison shows that the regulatory standards include more specific recommendations on the design and methods of studies, in addition to requirements to assure academic quality. The regulatory standards are more prescriptive or normative compared to the academic standards. Also, when uncertainty or controversy exists on methodology in the academic field, the regulatory standard sometimes simply recommends not to use the methods at this moment or recommends certain methods without a sound theoretical justification. Regulatory standards tend to make more explicit and straightforward recommendations, such as the value of the discount rate, and the Australian recommendation about CBA and indirect costs.

While regulatory standards often include prescriptive items, which may be important for the particular regulatory authority, these normative items are not appropriate for the quality review of our sample of PE studies. A study may not meet a normative guideline yet still be a high quality study. For example, a study could be high quality, even with a discount rate of 4% (if there is enough justification for this rate), although some regulatory guidelines recommend 5% (Canada, Australia) and the another recommends 6% (U.K.). Similarly, a study might not maintain equity among different socioeconomic groups in the analysis, but could be a good quality study if it conforms to its purposes. Also, a study's calculated costs can be credible without using "standard" costs.

Another example is viewpoint; a study can still be high quality, regardless of the viewpoint adopted, if the analysis is consistent with the viewpoint selected.

Our selection of review criteria therefore excluded items considered normative in Table 2. The starred items in Table 2 are those only found in the regulatory standards when compared to the academic standards based on Drummond et al. and Udvarhelyi et al. We excluded the following items, for the reasons indicated. "Effectiveness not efficacy should be captured" (〈*Outcome*〉-2) is more of a quality concern, but effectiveness is difficult to measure credibly in certain cases. In addition, this item is not found in the two academic standards. We therefore regarded this item as less important and excluded it from the quality review criteria. "Effectiveness should be proven/established (substantiated)" is another item that arises from a quality concern, but it is difficult to judge when this is fulfilled, as shown in the next item. For "Recommended/required data sources for outcomes", the data needed for substantiation differ widely among guidelines. The FDA guidelines require 2 or more randomized controlled trials (adequate and well-controlled trials), whereas the U.K. guidelines accept observational studies. Since the data needed for substantiation are controversial, we did not include this item. We also excluded the item in 〈*Discounting*〉, "Justification of the discount rate required", because the value of the discount rate is controversial and can be difficult to be justify theoretically. Moreover, justification of the discount rate is unnecessary if a fixed rate is recommended by mandatoryguidelines.

This selection process yielded 15 items for the quality review criteria (see **Table 3**). Table 2 includes additional instructions on the review criteria in parentheses to clarify the meaning of certain criteria.

Results of the Review of Japanese PE studies

Two of the authors (MM and SI) independently conducted the review for our sample of 10 retrieved articles, using the review criteria listed in Table 3. Disagreements between the review results were resolved by means of joint discussion and reevaluation. The choice for each question was Yes, No. The results of the review are presented in **Table 4**. As shown in Table 4, only 20% of the studies stated the viewpoint of the analysis. Approximately 70% of the studies with differential timing did discounting for costs and approximately 60% did discounting for outcomes. Sensitivity analysis was performed for 60% of all studies.

(1) Comparison with a similar U.S. study

We partly compared the results of this study to a similar quality review study conducted by Udvarhelyi et al.[3]. That paper reviewed 77 articles on the economic analyses of health services conducted between 1978-1987

(for the U.S.). The results of the comparison of these two review studies are shown in **Table 5**.

This comparison shows that our sample ranked higher on two criteria (sensitivty analysis, and discounting) and showed similar scores on one criterion (viewpint clearly stated). This comparison also identifies areas for improvement that are essential for assuring the quality of the studies. For example, the viewpoint of the analysis should be clearly stated for choosing appropriate costs, outcomes, and other important parameters, but only 20% of the Japan studies met this criterion. Similarly, discounting and sensitivity analysis are essential for good economic analysis, yet 40% of the sample did not perform any sensitivity analysis for key parameters and 36% did not carry out appropriate discounting. Udvarhelyi et al. [3] commented on their results, "Unless the use of appropriate methods for economic analysis improves, incorporating the results of economic analyses into policy making at either the public policy or clinical level may not result in increased efficiency of the health care system." A similar comment also applies to the results of our assessment of Japan-based PE studies.

Table 3 Criteria for Quality Review

1	Is the viewpoint of the analysis clearly stated ?
2	Are important comparators included (to fulfill the purpose of the study) ?
3.1	Are all costs relevant to the objective of the analysis included ? (Are all important items according to tce study perspective included, such as direct medical, direct nonmedical and indirect costs ? If some costs are not included, is there a discussion of the reasons ?)
3.2	Are all the cost items measured credibly by natural physical unit ? (Are costs items necessary for each alternative shown clearly and justified through expert panels, literature, etc ?)
3.3	Are monetary values for the physical units valued credibly ? (Are sources of these values stated ?)
4	Are all outcomes relevant to the objectives of tce analysis included ? (Are all possible effects including both positive and negasive effects considered ?)
5.1	Is discounting for future costs done, if necessary ?
5.2	Is discounting for future outcomes done, if necessary ?
6.1	Is any sensitivity analysis performed for any of the ranges of values for key parameters ?
6.2	Is sensitivity analysis performed on the discount rate ?
6.3	Is sensitivity analysis performed for the range of values for all key parameters ?
6.4	Is the range of values used in sensitivity analysis justified ? (Are persuasive ranges such an confidence intervals used ? or are the sources from which the ranges are derived shown in the analysis ?)
7	Are summary ratios from the analysis provided ?
8	Is incremental analysis performed, if necessary ?

(2) Comparison between different year groups

The published year of the 10 articles ranges from 1985 to 1993. We divided them into two groups of 5 articles each according to the year of publication (5 articles in 1985-1990, and 5 articles in 1991-1993). We compared the quality review results for each criteria for the two groups. For some criteria such as discounting and sensitivity analysis, the later group (1991-1993) seemed to conform better to the standard. This result may reflect recent improvements in the quality of Japan based PE studies.

(3) Comparison between different language groups (Japanese, English)

The sample includes 3 articles published in English. We examined whether a quality difference existed between the two language groups, arising perhaps because of higher quality standards required for publications in non-Japan based journals. The comparison of quality review results for each criteria showed no clear trend for Japanese versus English publications.

Other Characteristics of Japan-based PE Studies

We reviewed the sample of 10 Japan-based PE studies according to 8 other criteria in order to describe the characteristics of recent Japanese studies in the field of pharmacoeconomics, even if the data are not directly related to quality. This description may provide useful information about the status quo of Japan-based PE studies and about areas for improvement.

(1) Type of analysis

The most frequently found type of analysis is CEA (6 out of the 10 studies). The sample included one CUA, which was published recently[13]. The paper did not provide details on the method of utility measurement, but the paper used a formula established by Drummond et al [2] rather than designing a new measure.

(2) Perspective

In most cases, the studies did not specify the perspective of the analysis, as already stated. For the 2 articles in which the perspective was given, both were from the payer's perspective (that is, the government, in the case of Japan).

(3) Comparators

The studies used either current standard therapies or do-nothing as the comparator. No article specified whether the therapy used in the analysis is the cheapest alternative or not.

Table 4 Results of Quality Review of Japan-based Pharmacoeconomic Studies

Criteria for Review*		1	2	3.1	3.2	3.3	4	5.1	5.2	6.1	6.2	6.3	6.4	7	8
Author, Year	Language														
Fujino et al, 1985	English	N	Y	Y	N	Y	N/A	Y	N/A	Y	N	N	N	N/A	N/A
Sasaki & Eisenberg, 1987	English	Y	Y	N	Y	Y	Y	N/A	N/A	Y	N/A	Y	Y	Y	N
Fujino et al, 1988	Japanese	N	Y	Y	Y	Y	Y	N/A	Y	N	N	N	N	Y	Y
Fujino et al, 1989	Japanese	N	Y	N	N	Y	N	N	N	Y	N	Y	N	Y	Y
Baba et al, 1990	Japanese	N	Y	N	N	Y	N/A	N	N	N	N	N	N	N/A	N/A
Hayashi et al, 1991	English	N	Y	Y	N	N	Y	N/A	N/A	N	N	N	N	N	N
Hishihara, 1991	Japanese	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Fujino et al, 1992	Japanese	N	Y	N	Y	Y	Y	Y	N	Y	N	Y	N	Y	Y
Fujino et al, 1993	Japanese	N	Y	Y	N	N	Y	Y	Y	N	N	N	N	Y	Y
Habu et al, 1993	Japanese	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
YES(%)		20	100	60	50	80	88	71	57	60	22	50	20	88	75

(Y: Yes, N: No, N/A: Not applicable)

*Note: For a list of the criteria for review, see Table 3

Table 5 Comparison with the U.S. Study Result by Udvarhelyi et al.

		Japan	U.S.
1	Viewpoint clearly stated ?	20%(2/10)	18%(14/77)
5	Discounting done ?	64%(9/14)*	48%(14/29)
6.1	Sensitivity analysis done ?	60%(6/10)	30%(23/77)

* : 71%(5/7) for costs, 57%(4/7) for outcomes

(4) Time horizon

The time horizon chosen greatly affects the estimates of outcomes and costs, and the results of the analysis. The appropriate time horizon differs according to the type of pharmaceutical. If the drug effects extend to the future and if they are not negligible, then a longer time horizon to cover these effects should be adopted. Since the time horizon chosen greatly changes the results, a good justification for the choice is important. More than half of the studies in our sample, however, did not provide a good justification for the choice of time horizon.

(5) Type of outcomes

In 4 out of the 6 CEAs in our sample, life-years (lives saved) are used. Other types of outcomes used are the incidence of a disease and the rate of seroconversion.

(6) Discount rate

For the 5 articles that used discounting, the discount rate ranged from 3% to 5%.

(7) Sources of data

The studies in our sample used various sources of data. Many randomized controlled trials (RCTs) are available in Japan, mostly from drug approval data (usually published), but most RCTs provide information only about short-term use. To estimate the long-term effects of a drug, a study needs data collected on a long-term basis, such as a large-scale epidemiological study. But such studies are not commonly available in Japan. As a result, many Japan-based studies use foreign study results or expert opinions (probably not study-based).

(8) Sources of costs

The only available data source for cost valuation in Japan is the government's fee schedule for reimbursement. This schedule is appropriate if the perspective is the payer's. If a societal perspective is attempted, however, then there is no appropriate existing data source for costs in Japan.

[Discussion]

Efforts to assess the quality of PE studies in Japan are only just beginning. One quality review of Japanese technology assessments was conducted by Kamae et al. [30], but the source of the reviewed studies is limited (studies performed as Kosei Kagaku Kenkyu, which is funded by the Ministry of Health&Welfare for health and welfare related scientific research), and the sample is not focused on PE studies. Moreover, Kamae et al. compared their analysis to that performed by Drummond et al. [2], although articles selected by Drummond et al. were not randomly selected. The small number of studies in the field of technology assessment in Japan may be due to the lack of incentives for this kind of analysis. In the health field, the nation-wide fee schedule

system for reimbursement has reduced the incentive for providers to evaluate the cost-effectiveness of medical technologies. However, because of soaring health care expenditures in Japan (24.4 trillion yen in 1993), the economics of medical services (including pharmaceuticals, which account for about 30% of government health expenditures) is attracting greater attention, particularly from the government (the payer). Under these circumstances, the cost-effectiveness of pharmaceuticals is becoming a major issue for all the parties concerned (e.g., the Ministry of Health and Welfare, the pharmaceutical industry, the physicians, the hospitals, and other health care players). The international trend of requiring medical technology assessment in drug approval processes may also create an incentive for leading Japanese pharmaceutical companies to consider the importance of PE studies.

This review of Japan-based PE studies found them to be comparable in some aspects to the U.S. -based studies reviewed by Udvarhelyi et al. [3], although these two samples are not fully comparable. The results indicate a low level of quality for the Japanese analyses with substantial problems for several important elements of economic analysis (e.g., the lack of an explicit analytic framework, especially the analysis objective and the standpoint of the analysis). More recent articles seemed to be of higher quality, but no reliable trend was found in the group analyses.

A major finding, and a major limitation, of this quality review, is the small number of articles retrieved. This probably reflects the immaturity of this field in Japan. Moreover, half of the analyses retrieved were performed by the same senior author.

If PE analyses are intended to be used in resource allocation decisions, then the quality of the studies should be improved in the United States and in Japan[3]. Government regulatory guidelines (either voluntary or mandatory) could be effective in promoting a proper methodology for regulatory purposes and for academic researchers. Other kinds of government intervention, such as establishing PE study groups and providing funds for PE studies, could also be useful. If PE studies are to play a role in health policy making (e.g., on pricing decisions) in Japan, then it is essential to train more experts in this field (both as researchers and as reviewers) and to develop regulatory guidelines.

Although PE studies are not mandated in Japan, some pharmaceutical companies have begun to perform economic evaluations of their products, and are submitting these studies in supporting documents for pricing decisions. The current lack of a standardized method or implicit consensus on the methodology may prevent an efficient use of these study results. The Japanese government, therefore, may need to provide some guidance to standardize these studies so that they can be effectively used in decisions about pricing.

A number of questions need to be addressed before official guidelines on PE studies are developed in Japan. For example, what structure should the guidelines take, and what elements should be included? For the latter question, one starting point could be the elements identified in this study's development of quality review criteria. However, the structure and contents of guidelines for PE studies greatly depend on the purposes. If Japan decides to develop guidelines to regulate economic analyses used for pricing decisions, then the government will need to obtain particular information from these analyses, and the appropriate structure would probably be more like the Canadian or Australian guidelines than the U.S. FDA or the U.K. guidelines.

How the study results should be used for pricing decisions should also be discussed thoroughly. Should the price be fixed so that it would be the least cost alternative? Or should the drug be removed from the price list if other alternatives are significantly more cost-effective? These policy decisions depend on political judgment, although an academic discussion of the substantive issues can help inform the decision makers.

The consequences for industry of mandatory guidelines have not been fully evaluated, even in Australia or Canada, and this question deserves more study. Mandatory guidelines create an additional burden for pharmaceutical manufacturers, but there may also be some benefits for some firms. The efficiency of having mandatory guidelines should also be carefully considered in the discussion about guideline development in Japan.

The limitations of official guidelines should also be recognized. Guidelines inevitably have only a limited role in setting explicit and transparent standards. Investigators still must be versed in economic analysis in order to perform high quality studies. Because Japan has only a limited number of experts engaged in this field, the training of experts may be the most important action to be taken beyond the development of official guidelines.

This quality review has a number of limitations. First, some information needed for quality assessment was sometimes not provided in the published study. In such cases of missing information, we assumed that the criterion was not fulfilled, in order to be conservative.

A second limitation is the lack of comparable review results. We used the results from a review article by Udvarhelyi et al. [3] but this sample includes older studies (1978-1987) compared to our sample (1985-1993). Also,

the studies used in Udvarhelyi's review are not limited to PE studies, which could affect the comparison. In a future study, it may be useful to develop a fully comparable sample of U.S. articles using the same years and limited to PE studies, and then apply the same quality review criteria to the U.S. papers.

A third limitation of this review is the small number of Japan-based PE studies in the sample, due to the inefficiency of the database retrieval systems or the scarcity of published papers in this field in Japan. This small sample size makes it difficult to perform statistically reliable analysis. In addition, there is a possibility of publication bias, since the articles collected may not be representatives of the real population of PE studies (both published and unpublished), which may lower the validity of the review.

A fourth limitation results from our efforts to improve the study's reliability by applying the review criteria as consistently as possible. For example, in judging if all relevant costs were included, we answered "Yes" if the authors gave any justification about including or excluding some costs, even if the justification was not fully persuasive. Consequently, the articles with a higher number of "Yes" answers may not necessarily give reasonable or credible analysis results.

Lastly, the authors would like to state that the review criteria we developed represent an initial effort and should not be viewed as either comprehensive or final. The review criteria may not detect all aspects of the quality of a study. In addition, it should be noted that we did not intend to evaluate the entire value of each study.

Conclusion

This study represents the first systematic assessment of the quality of Japan-based PE studies, and provides an evaluation of the development of this field in Japan. Our sample of 10 PE studies was obtained through an extensive search of four major English and Japanese databases of medical journals and through a non-database search. The review of these 10 studies showed that the quality of the Japan-based PE studies is not very high, although the quality may be similar to a partially comparable sample of U.S. -based studies. The review also identified specific areas to be improved in the field of pharmacoeconomics in Japan.

The development of official PE guidelines could help improve the quality of PE studies in Japan. However, in setting up Japanese guidelines for health policy decision making, a number of methodological and policy issues need to be discussed thoroughly, taking into account the experiences of other countries.

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An Analysis of Pharmacoeconomic Studies in Japan

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本研究では、わが国で過去に報告された医薬品経済評価論文を収集し、体系的なレビューを試みた。文献収集は、医学文献データベース等を用いて行い、10文献が収集された。レビュー項目は、医療技術経済評価に関する文献および教科書がオーストラリア・カナダ・英国・米国における医薬品経済評価ガイドライン等を参考に決定した。今回の分析結果を米国における医療技術経済評価論文のレビュー結果と比較したところ、1項目については米国と同様の問題が存在していたが、他の2項目については米国よりも結果が優れていた。また、今回収集した論文の大部分において、「分析視点の明確化」や「割引率の感度分析」といった、医薬品経済評価研究において重要な項目のいくつかが欠如していることが明らかとなった。

〔キーワード〕
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