Cost-Effectiveness Analysis of Oseltamivir for Influenza Treatment Considering the Virus Emerging Resistant to the Drug in Japan

Hiroko Nagase, PhD,1 Kensuke Moriwaki, MS,1 Maki Kamae, MD, MPH,2 Shinichiro Yanagisawa, PhD,3 Isao Kamae, MD, DrPH1,4
1Division of Medical Statistics, Graduate School of Medicine, Kobe University, Kobe, Japan; 2The Center for the Evaluation of Value and Risk in Health, Tufts Medical Center, Boston, MA, USA; 3Division of Medical Economics, School of Pharmacy, Himeji Dokkyo University, Himeji, Japan; 4Graduate School of Health Management, Keio University, Keio, Japan

ABSTRACT

Aim: The purpose of this study is to evaluate the cost-effectiveness of oseltamivir for influenza in Japan considering the complications and the emergence of oseltamivir-resistant virus.

Methods: Study design is a cost-effectiveness analysis in decision analytic modeling based on previously published evidence. Outcome measures included costs and quality-adjusted life year (QALY).

Results and Conclusion: In the base-case analysis, the incremental cost-effectiveness ratio (ICER) of oseltamivir during influenza and complications was JPY398,571 ($3320) per QALY without productivity loss, which implied oseltamivir is evidently cost-effective. Furthermore, considering the productivity loss, the ICER for oseltamivir turned to be negative, which means simply dominant. When the prevalence was in the low range of 10% to 38%, oseltamivir became less cost-effective than conventional treatment. Regarding potential emergence of the drug-resistant virus, we found the dominance of oseltamivir will vanish if the emerging rate becomes larger than 27%. The two-way sensitivity analysis also suggested that if the resistant virus rate becomes less and the prevalence higher, then oseltamivir becomes more advantageous. The analysis for uncertainty, using cost-effectiveness acceptability curve by Monte Carlo simulation, resulted in the estimate of about 80% chance that oseltamivir could be cost-effective at the willingness-to-pay level of JPY6,000,000 ($50,000), which is commonly accepted as an affordable threshold.

Keywords: cost-effectiveness analysis, influenza, oseltamivir.

Introduction

Influenza is a common viral respiratory infection that typically occurs in winter. Each year in Japan, a 5% to 10% fraction of people gets infected with influenza, resulting in about 1000 to 2000 deaths by influenza and 5000 deaths due to complications such as pneumonia. Most of the fatal cases are the elderly over 65 years old and patients with high risk. An about 20% to 25% fraction of the elderly infected with influenza is estimated to develop pneumonia, and 5% of those patients will be dead [1–3]. The annual incident rate of influenza in children is estimated to be 1.5 to 3.0 times as high as that in adults [4].

It is demonstrated that the treatment with the neuraminidase inhibitors such as oseltamivir and zanamivir reduced the duration of influenza symptoms in adult patients by 1 to 1.5 days [5–8]. In addition, both drugs reduced the incidence of complications requiring for antibiotics [5,8–10]. In Japan, oseltamivir is approved in patients: 1) symptomatic for no more than 2 days and 2) diagnosed for influenza by the rapid test. The combination of the rapid diagnostic test and a subsequent prescription of oseltamivir costs JPY6250 ($52.00) [11] per primary dose per patient. Then, the total national expenditure for oseltamivir in Japan has become an economic burden since oseltamivir has been prescribed for 35 million people these 5 years.

An etiological concern has been also raised about emerging of drug-resistant virus (DRV) [12].

According to those concerns, the following questions were raised in our study: 1) is oseltamivir cost-effective in the Japanese setting, taking complications into account? and 2) with regard to the emerging DRV, how does it affect the cost-effectiveness of oseltamivir? The objective of our study is to address these questions, using a decision analytic modeling.

Method

Modeling and Assumptions

We modeled a decision tree (Fig. S1) comparing two strategies: 1) with rapid diagnostic testing followed by treatment with oseltamivir, and 2) without testing followed by conventional treatments without oseltamivir. The conventional treatments include a dose of febrifuge such as acetaminophen. The probabilities assigned to the decision tree are shown in Tables S1 and S2. In Figure S1, emerging of the DRV is represented at a chance node employing the efficacy of oseltamivir for the DRV. Outcomes were measured with the quality-adjusted life years (QALYs) and the costs. The time horizon for the analysis was set in 53 days.

The prevalence of influenza, 60%, among the patients with symptoms of influenza-like illness is shown in Table S1 [13,14]. The frequency of common secondary complications of influenza is collected in the trials and other published data and shown in Table S2 [1,10,15–18].

The costs assigned to the model are listed in Table S3 [11,19,20]. This analysis includes not only estimates of direct medical costs but also of productivity loss due to influenza and pneumonia.

To see Tables S1 and S2 and Figures S1 and S2, see Cost-Effectiveness Analysis of Oseltamivir for Influenza Treatment Considering the Virus Emerging Resistant to the Drug in Japan Value in Health Supporting Information, Part I at: http://www
ispor.org/Publications/value/ViHsupplementary/ViH12s3_Nagase.asp.

The productivity loss due to influenza was estimated with JPY34,770 ($290.00) for oseltamivir and JPY39,618 ($330.00) for conventional treatment by using the days needed to return to normal activity, and by converting the estimated days into monetary value based on the average gross Japanese income [21,22]. The productivity loss of hospitalization due to pneumonia was also estimated with JPY91,808 ($765) for the elderly and JPY180,804 ($1507) for adults under 64 years based on these assumptions (see Cost-Effectiveness Analysis of Oseltamivir for Influenza Treatment Considering the Virus Emerging Resistant to the Drug in Japan Value in Health Supporting Information, Part I at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Nagase.asp).

Since the availability of utility data was limited in Japan, the foreign literature [10,23] was employed to set the baseline values in health-related quality of life due to influenza infection shown in Table S4.

Figure S1 and Tables S1–S4 are shown in Cost-Effectiveness Analysis of Oseltamivir for Influenza Treatment Considering the Virus Emerging Resistant to the Drug in Japan Value in Health Supporting Information, Part I at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Nagase.asp.

Analysis

Please see Cost-Effectiveness Analysis of Oseltamivir for Influenza Treatment Considering the Virus Emerging Resistant to the Drug in Japan Value in Health Supporting Information, Part II at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Nagase.asp.

Results

Base-case Analysis

Table S5 shows the main results in the form of cost-effectiveness table. Without productivity loss, the total cost of oseltamivir per one patient was estimated as JPY13,548 ($113), and JPY13,269 ($111) for conventional treatment. Using the utility data at Table S4, the oseltamivir regimen earned 0.1381 QALYs and the conventional treatment with 0.1374 QALYs. The incremental cost-effectiveness ratio (ICER) of oseltamivir versus the conventional treatment without productivity loss was estimated as JPY398,571 ($3320) per QALY. On the other hand, considering the productivity loss during the hospitalization due to pneumonia, the ICER was changed to be negative, which means simple dominance of oseltamivir over conventional therapy. Especially for the elderly, the ICER for oseltamivir is simply dominant even if the productivity loss was not included as shown in Table S6.

To see Tables S5 and S6, see Cost-Effectiveness Analysis of Oseltamivir for Influenza Treatment Considering the Virus Emerging Resistant to the Drug in Japan Value in Health Supporting Information, Part II at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Nagase.asp.

Sensitivity Analysis

Regarding the sensitivity analysis on prevalence of influenza, the dominance of oseltamivir vanished when the prevalence was under 39% for the case with productivity loss shown in Figure S2a.

The result of sensitivity analysis on the rapid diagnostic test showed that the dominance of oseltamivir vanishes when the sensitivity of the test becomes fewer than 60%. Figure S2b shows the result of two-way sensitivity analysis by prevalence of influenza and the sensitivity of the diagnostic test. That is, the treatment with oseltamivir becomes dominant when the sensitivity of the rapid test is higher than about 60% in the period of epidemics (prevalence: more than 70%), and also when the sensitivity is higher than 90% in the period of nonepidesms (prevalence: less than 40%).

Regarding the emerging DRV, we examined how much the effectiveness of oseltamivir would be reduced by the DRV. Then, we found the dominance of oseltamivir vanishes if the emerging rate of DRV is larger than 27% shown in Figure S3a. In the two-way sensitivity analysis on prevalence and the emerging rate of DRV, the emerging rate of the DRV had more influence in the nonepideemic season rather than epidemic season. Therefore, if we could get the less DRV rate and the higher prevalence of influenza, oseltamivir would be the more advantageous. The joint effect in detail is shown in Figure S3b.

The results of the probabilistic sensitivity analysis are shown in Figure S4. Figure S4a illustrates the 95% confidence eclipse located at the North-East and South-East quadrants in a condensed form. In more details, a 57.86% portion at the North-East quadrant and 20.24% at the South-East of the plotted pairs were under the line with the slope of JPY6,000,000/QALY ($50,000/QALY), which is generally accepted as willingness-to-pay (WTP) for medical technologies in Japan [24]. The similar information as in Figure S4a, but in different shapes, is shown as the cost-effectiveness acceptability curve in Figure S4b comparing two curves for the oseltamivir to conventional treatment. At the graph, a threshold of JPY6,000,000/QALY on the horizontal axis corresponds to about 80% probability of having better cost-effectiveness.

To see Figures S2–4, see Cost-Effectiveness Analysis of Oseltamivir for Influenza Treatment Considering the Virus Emerging Resistant to the Drug in Japan Value in Health Supporting Information: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Nagase.asp.

Discussion

This study began with two questions about: 1) cost-effectiveness of oseltamivir in the Japanese setting, considering the duration of complications and 2) the degree of impact caused by the DRV on the cost-effectiveness. The first question was motivated by the fact that, with quite a few studies from Japan reporting the crude estimate of costs on oseltamivir, no cost-effectiveness analysis was conducted, in any details, bringing into focus the complications after acute phase of the treatment. Hence, our decision tree modeled three groups of children, adults, and the elderly, each of which has possibilities leading to two categories of complications: pneumonia and the others. As a result, the ICER was eventually estimated at JPY398,571/QALY ($3320/QALY), costing without productivity loss, for the screening group followed by oseltamivir therapy. This primary result of our study suggests that, when considering the complications, it is very cost-effective, compared to a threshold of JPY50,000/QALY commonly accepted to be cost-effective in medical technology assessment [25]. It implies that oseltamivir may be useful in economic terms in order to reduce a high proportion of hospitalization for the elderly in Japan due to the complication of pneumonia.

The advantage of good cost-effectiveness in the oseltamivir therapy becomes more evident when we consider the productivity loss in costing. The ICER in such a case turned to be negative, which means that the strategy with oseltamivir is simply dominant over the one without oseltamivir. Accordingly, oseltamivir is recommended regardless of the perspectives in analysis, whether
with productivity loss or without it, which represents the perspective of payers or society, respectively. Such a robustness of the ICERs over different perspectives, estimated in this study, may justify the positive listing of oseltamivir in the Japanese health insurance system of government since the system has a universal coverage and premiums for all of the Japanese.

One of the concerns is uncertainty around the point ICER estimate even if it is a good estimate. A problem-solving approach for this concern is the probabilistic sensitivity analysis shown in Figure S4. In this figure, the scattered plot and also the cost-effectiveness acceptability curve seem to be in good shape, suggesting that the oseltamivir group would be regarded as more cost-effective at the chance of 78.1%, compared to the ratio of JPY6,000,000/QALY ($50,000/QALY).

The recommendation for oseltamivir being favorable should be carefully denied according to the results of sensitivity analyses. The simplest rule of thumb is that the indication of oseltamivir is not encouraged at the early or late stage of the epidemic when the prevalence of influenza becomes lower than about 40% as illustrated from the one-way sensitivity analysis in Figure S2a. Also, Figure S2b gives further information to physicians and public health professionals how they could assess the change of oseltamivir’s dominance with respect to the interaction of two factors such as the sensitivity of the rapid diagnostic test and the prevalence of the disease. To see Figure S2a and b, see Cost-Effectiveness Analysis of Oseltamivir for Influenza Treatment Considering the Virus Emerging Resistant to the Drug in Japan Value in Health Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Nagase.asp.

As the sensitivity of the test varies around 50% to 70%, taking into account the worst value of 50%, then Figure S2b indicates the prevalence must be maintained at least around 70% so that the dominance of oseltamivir could be accomplished at the satisfactory level. Based on this evidence, physicians should carefully identify the high-risk group with the prevalence of 70% or higher before taking the rapid diagnostic test followed by the oseltamivir therapy.

Regarding the second question, we obtained a threshold of 27% for the emerging rate of DRV, at which the expected values of cost-effectiveness for two strategies cross over as shown in Figure S3a. Figure S3b gives further information on the two-way sensitivity analysis, as well as Figure S4b. It suggests that the epidemiological evidence on the drug-resistance rate is crucially important to assess how much the oseltamivir therapy can provide us with cost-effectiveness benefit under the circumstance of changing prevalence in the epidemic period. It is a challenge for physicians to control and suppress the rate of DRV around or under 45% so that the benefit of oseltamivir may not be lost even at the peak stage of epidemic with the prevalence of 90% shown at the bottom right of Figure S3b. As there is a concern about high possibility that the wide spread of the drug-resistant H1N1 influenza virus might occur in Japan [26], our result would be useful for public health decision-making when the DRV is spread in the near future. To see Figures S3a and b and S4b, see Cost-Effectiveness Analysis of Oseltamivir for Influenza Treatment Considering the Virus Emerging Resistant to the Drug in Japan Value in Health Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Nagase.asp.

On the other hand, our analysis is subject to a number of limitations, including scarce availability of Japanese evidence on probabilities and utilities. Despite the effort finding relevant literature, the baseline probabilities for the analysis were employed from a few articles such as the Japanese clinical trials and the systematic reviews on the literature published in Western countries. Consequently, a selection bias of evidence might be inevitably, to some extent, contained in the baseline analysis. The utility assessment in our study is also limited with the same reasons. To overcome the limitation with no utility values available for Japanese, we assumed unbiased transferability of evidence from foreign countries to the Japanese setting. Such limitations on data availability, of course, become a potential threat to external validity of our study. Therefore, the validation of our modeling based on the original data in Japan remains for further investigations.

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References