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ORIGINAL ARTICLE

Estimating the cost-effectiveness of linezolid for the treatment of methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia in Taiwan

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Abstract *Background/Purpose:* Methicillin-resistant *Staphylococcus aureus* (MRSA) nosocomial pneumonia (NP) is associated with higher resource utilization, increased hospital stays, and mortality. We present a health economics model to understand the impact of using linezolid as the first-line treatment of MRSA NP in Taiwan.
Methods: We developed a cost-effectiveness model to estimate the costs and clinical outcomes of using linezolid 600 mg b.i.d. versus vancomycin 15 mg/kg b.i.d. as the first-line treatment of MRSA NP in Taiwan. The model is a decision-analytic analysis in which a MRSA-confirmed patient is simulated to utilize one of the treatments, using data from a clinical trial. Within each treatment arm, the patient can or cannot achieve clinical cure. Regardless of whether the clinical cure was achieved or not, the patient may or may not have experienced an adverse event. The per-protocol results for clinical cure were 57.6% and 46.6% for linezolid and vancomycin, respectively.

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Results: The total cost of linezolid was $376 more per patient than that of vancomycin. Drug costs were higher for linezolid than for vancomycin ($1108 vs. $233), and hospitalization costs were lower ($4998 vs. $5496). With higher cost and higher cure rates for linezolid, the incremental cost per cure was $3421.

Conclusion: This study projects linezolid to have higher drug costs, lower hospital costs, and higher overall costs compared with vancomycin. This is balanced against the higher clinical cure rate for linezolid. Depending on the willingness to pay for clinical cure, linezolid could be cost effective as the first-line treatment of NP in Taiwan.

Introduction

Hospital-acquired pneumonia or nosocomial pneumonia (NP) is characterized by the pneumonia that a patient acquires 2 days or 3 days after being admitted to the hospital. Methicillin-resistant *Staphylococcus aureus* (MRSA) is responsible for many cases of NP in Taiwan.[1] This disease is associated with higher resource utilization, increased hospital stays, and mortality.[2] A recent study in Taiwan suggests an excess 1-year mortality of 20.2% for patients with *S. aureus* health care-associated infections, as well as increased ventilator dependence and dialysis.[3]

Vancomycin, a glycopeptide antibiotic, has been the standard of care since the 1980s for treating NP in Taiwan. Typical treatment regimens include using vancomycin from empiric treatment through confirmation, but recent findings suggest that doing so may be suboptimal.[4] Not only is vancomycin associated with nephrotoxicity, but there have also been reports that vancomycin-nonsusceptible organisms are becoming more common.[5] Teicoplanin, a semisynthetic glycopeptide antibiotic, has also been used in a manner similar to vancomycin. Recently, linezolid, the first member of the oxazolidine class of drugs, has been recommended as one of the antibiotics of choice for treatment of MRSA pneumonia, both in the United States and in Taiwan.[6]

In this study, we present a health economics and outcomes research (HEOR) model to understand the impact of using linezolid as the first-line treatment of MRSA NP in Taiwan. HEOR provides a model framework to understand the tradeoffs between competing options—in this case, vancomycin versus linezolid. The tradeoffs include costs (e.g., hospital utilization, pharmacy costs, and laboratory tests) and outcomes (clinical cure) associated with treatment choices. HEOR models include cost-effectiveness studies, which estimate the value for money of new treatments on a per-patient basis using common units, such as clinical cure, progression-free survival, and life years. The output expresses the incremental cost-effectiveness ratio (ICER) of the competing treatments.

Health technology assessment (HTA) committees often consult HEOR studies in their evaluations. The ICERs from cost-effectiveness analyses can be used by HTA bodies to support inclusion or exclusion recommendations of new treatments in health systems. For example, HTAs may have ICER thresholds above which treatments are not considered to be cost effective and thus are not recommended for reimbursement. Some HTAs utilizing this type of analysis include the National Institute for Health and Clinical Excellence in the United Kingdom, Blue Cross Blue Shield's Technology Assessment Committee in the United States, and the Center for Disease Evaluation in Taiwan.[7] To evaluate new technologies, the Center for Disease Evaluation conducts systematic reviews of reports from other HTA agencies, but they also recommend studies based on local, Taiwanese data. The model presented in this study is a localized HEOR model for the treatment of MRSA NP in Taiwan.

Methods

Model overview

We developed a cost-effectiveness model in Microsoft Excel (Microsoft Inc., Redmond, WA, USA) to estimate the costs and clinical outcomes of using linezolid 600 mg b.i.d. versus vancomycin 15 mg/kg b.i.d. as the first-line treatment of NP in Taiwan. We based the analysis on the results of the ZEPHyR (Linezolid in the treatment of subjects with nosocomial pneumonia proven to be due to methicillin-resistant *Staphylococcus aureus*) clinical trial, a randomized, double-blind, multicenter study. Note that the trial was global, with patients being enrolled at various sites in the United States, Europe, Asia, South America, and other regions. For additional details on the patient demographics, we refer readers to the original trial publication.[8] The assessment was conducted from a payer's perspective, and the timeframe is the same duration of the end of study in the trial, 7–30 days after end of treatment.

The final output is the incremental cost per cure (ICPC), which measures the additional monetary cost of achieving a clinical cure in an additional patient.

The model is a decision-analytic model the structure of which mimics that of the ZEPHyR clinical trial design (Figure 1). An MRSA-confirmed patient is simulated to utilize one of the following treatments: linezolid 600 mg b.i.d. or vancomycin 15 mg/kg b.i.d. Within each treatment arm, the patient can or cannot achieve clinical cure; in line with the trial protocol, clinical cure was defined as the resolution of clinical signs and symptoms of pneumonia, improvement or lack of progression in chest imaging, and
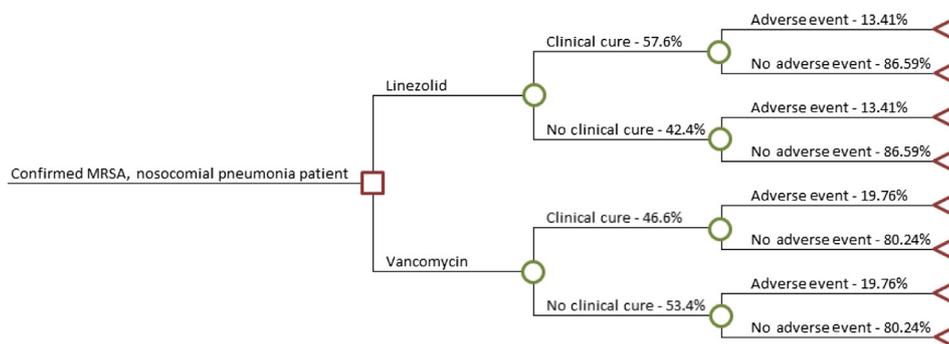
Figure 1. Decision-analytic framework. Rates of clinical cure and adverse events for linezolid and vancomycin were derived from ZyPHER study. MRSA = methicillin-resistant *Staphylococcus aureus*.

no requirement for additional antibacterial treatment at the end of the study. Regardless of whether the clinical cure was achieved or not, the patient may or may not have experienced an adverse event. The "adverse event" arm in Figure 1 includes events considered clinically important in the intent-to-treat population: anemia, renal failure/impairment/azotemia, cardiac arrest, thrombocytopenia, pancreatitis, polyneuropathy, pancytopenia/neutropenia, and paresthesia. The probability of each event is described in the following section.

Probabilities

Probabilities of clinical events were obtained directly from the clinical trial. Clinical cure rates were based on the primary endpoint, per-protocol results at the end of the study: 57.6% for linezolid and 46.6% for vancomycin. Probabilities of the adverse events are shown in Table 1. The aggregate adverse event rates for linezolid and vancomycin are 13.40% and 19.76%, respectively, which are the summation of the individual rates.

Costs

We used a microcosting approach by estimating the product of the utilization quantities and the unit costs. Based on an average of 10 days of treatment per patient in the ZEPHyR clinical trial, the total number of hospital and intensive

care unit (ICU) days were 17.2 days and 10.1 days for linezolid and 18.1 days and 10.6 days for vancomycin, respectively. While in the hospital, vancomycin-treated patients were tested daily for serum creatinine levels, serum vancomycin levels, and complete blood counts. Linezolid-treated patients were monitored for serum creatinine levels and complete blood counts. For both treatments, the number of physician visits per day during the inpatient stay was assumed to be one. If the patient experiences an adverse event, it results in additional 1.7 days in the general ward. Treatment failure led to additional 2 days in the general ward.[9−11]

Medication costs were derived from the National Health Insurance database, and were $55.40 and $11.67 for linezolid intravenous (IV) 600 mg and vancomycin 1 g, PDS (polydioxanone) IV, respectively. Treatment and utilization costs were estimated from public sources (Table 2). In our analysis, the increased costs associated with adverse events were assumed to be limited to costs incurred from the resulting additional length of hospital stay.

Sensitivity analysis

To examine the robustness of our results, sensitivity analysis was performed. We varied the clinical probabilities and costs by 5%, 10%, and 20%, and performed one-way sensitivity analysis. In the one-way sensitivity analysis, we changed a single parameter and calculated the resulting

Table 1 Probabilities of clinical cure and adverse events by linezolid and vancomycin, respectively.

Input	Linezolid (%)	Vancomycin (%)	Source
Efficacy (clinical success rate)	57.60	46.60	Clinical response rate—PP at EOS data
Adverse event rates			
Anemia	5.03	7.16	Clinically important investigator-reported
Renal failure/impairment/azotemia	3.69	7.33	all-cause AEs in the intent-to-treat population
Cardiac arrest	1.84	2.21	
Thrombocytopenia	1.34	2.21	
Pancreatitis	0.84	0.17	
Polyneuropathy	0.00	0.17	
Pancytopenia/neutropenia	0.67	0.34	
Paresthesia	0.00	0.17	

AE = adverse event; EOS = end of study; PP = per protocol.

Table 2 Unit costs for inpatient costs and associated laboratory works.

Input	Unit cost ($)[a]	Source
Inpatient cost/d (general ward)	76.85	Sheng et al (2005)[24] estimated inpatient costs, including accommodation & material/service costs
Inpatient cost/d (ICU)	419.6	Sheng et al (2005)[24] estimated inpatient costs, including accommodation & material/service costs
Lab work (serum creatinine levels)	1.33	NHIA website
Lab work (serum vancomycin levels)	10.67	NHIA website
Lab work (complete blood count)	6.67	NHIA website

[a] Costs were estimated in local currency of Taiwan and their values were converted to USD using the formula 1 USD = 30 TWD.
ICU = intensive care unit; NHIA = National Health Insurance Administration; TWD = Taiwan dollar; USD = US dollar.

ICPC based on the high and low estimates of that parameter.

Results

In the ZEPHyR study, characteristics of the patient populations between the linezolid and vancomycin arms were generally balanced with disproportionately more males and whites. In this base case, the total cost of linezolid was $376 more per patient than that of vancomycin (Table 3). Drug costs were found to be higher for linezolid than for vancomycin ($1108 vs. $233), and hospitalization costs were lower ($4998 vs. $5496). The per-protocol results for clinical cure at the end of the study were 57.6% and 46.6% for linezolid and vancomycin, respectively, statistically different at $p = 0.042$. With higher cost and higher cure rates for linezolid, the ICPC was $3421. With a conservative assumption of 14 days of treatment duration per patient, the ICPC was moderately increased to $6601.

The nondrug costs for linezolid were as follows: ICU $4238, ward (clinical cure) $546, ward (no clinical cure) $699, laboratory (clinical cure) $138, and laboratory (no clinical cure) $154. Costs for vancomycin were as follows: ICU $4448, ward (clinical cure) $576, ward (no clinical cure) $730, laboratory (clinical cure) $172, and laboratory (no clinical cure) $191. ICU charges accounted for the largest nondrug cost between the treatments, with vancomycin costing $210 more than linezolid.

Sensitivity analysis results

By varying the parameters by ± 5% individually, the ICPC ranges from $1714 to $5127, a spread of $3413 (Figure 2). Clinical parameters had the largest impact on ICPC, led by

the number of days in ICU and clinical cure rate: an increase in vancomycin ICU days decreases the ICPC and results in linezolid appearing relatively more cost effective. Cost components (i.e., drug costs, dosage, and treatment duration) did not influence ICPC as much as the clinical parameters. Variation in the cost of linezolid 600 mg from $52.63 to $58.17 changed the ICPC from $2917 to $3924. Similar hierarchies of parameter influence were observed by varying the parameters in the range of 10—20%.

Discussion

To our knowledge, this is the first study to evaluate the cost effectiveness of treating MRSA NP with linezolid versus vancomycin in Taiwan. The decision-analytic model was based on the ZEPHyR clinical trial, using clinical cure as the outcome. The results suggest linezolid to have higher drug costs, lower hospital costs, and higher overall costs compared with vancomycin. This is balanced against the higher clinical cure rate for linezolid, resulting in an ICPC of $3421. The finding that linezolid has higher costs and better outcomes is consistent with the previously published literature. Mullins et al[12] performed a claims database analysis in the USA and estimated $3600 as the incremental cost per life saved for linezolid. In addition, for the USA, Shorr et al[13] estimated the cost per quality-adjusted life year (QALY) of linezolid versus vancomycin to be approximately $30,000 and concluded it as a cost-effective treatment option. For Spain, Grau et al[14] and León et al[15] calculated ratios of €349 per QALY and €406 per life year gained, respectively. In Germany, Grünewald et al[16] constructed a decision analytic model based on the published sources and physician interviews, and their analysis suggests a ratio of €7756 per additional patient

Table 3 Base case results of incremental costs-effectiveness ratio.

Drug	Costs (USD)			Effectiveness	Incremental cost per cured person ($)
	Drug costs ($)	Hospitalization costs ($)	Total costs ($)	% of patients cured	
Vancomycin	233	5496	5729	47	—
Linezolid	1108	4998	6106	58	—
Incremental	−875	498	−376	−11	3421

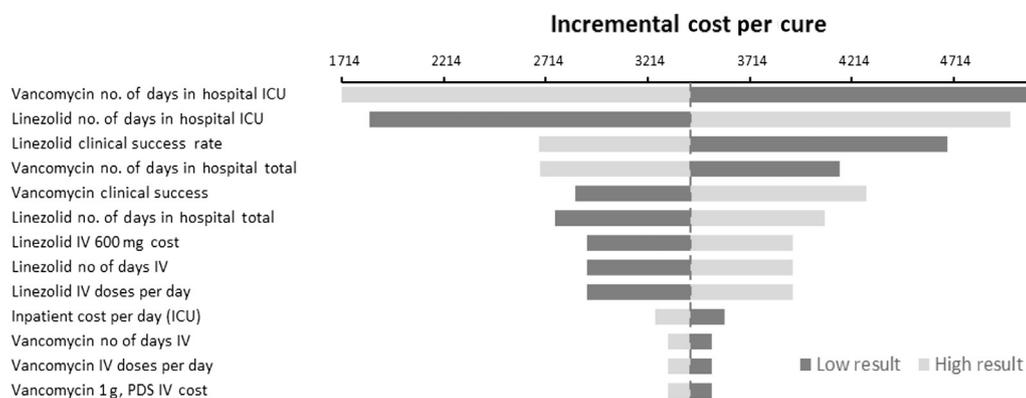USD = US dollar.

Incremental cost per cure

Figure 2. One-way sensitivity analysis by changing a single clinical parameter or cost. ICU = intensive care unit; IV = intravenous.

cured. In Argentina, Aiello et al[17] estimated the incremental cost per life year gained to be $482. In an analysis for France, De Cock et al[18] found linezolid to be cost saving as well as to have better clinical outcomes relative to vancomycin.

In our analysis, we used clinical cure as the effectiveness measure, because it was the primary endpoint of the ZEPHyR trial and the timeframe of the model was short, so life year measures would be difficult to forecast. This approach is consistent with that reported in papers in this disease area and others.[14] Using a disease-specific outcome measure, it is difficult to conclude whether or not the results are cost effective; to our knowledge, no research has been conducted regarding the willingness to pay of clinical cures for NP. World Health Organization guidelines suggest two to three times gross domestic product per capita as the appropriate threshold for considering a treatment to be cost effective.[19] In Taiwan, this range would be $42–63K[20] per life year saved. If we consider the lack of clinical cure to result in death within 1 year of the end of the clinical trial, our results would indicate linezolid to be cost effective because our ICPC is $3421, which is below the threshold range in Taiwan. However, without a translation to a common denominator such as a QALY, it would be difficult for payers to make coverage decisions across disease areas.

The short-duration timeframe stems from the choice of using the clinical trial protocol as the structure of the model. Like most economic models, this analysis is intended to be a parable of the disease area, and we balance the tradeoff between tractability and realism. This approach is in line with other studies in the field of health economics, which use clinical trial data in the model.[21,22] The alternative of using real-world data is also not without difficulties: each health system, hospital, and doctor may have a different way of treating the patient. Although the trial was conducted in multicenter, international settings, we acknowledge that it may not fully represent treatment patterns in Taiwan. For example, patients may have a longer length of stay because hospitals do not encourage discharge. Costs and utilization may vary across hospitals and regions. Moreover, we assumed that laboratory tests would be conducted in patients every day, which might not be the case in practice. The

sensitivity analysis suggests that the utilization and cost of laboratory work have very little impact on the final results. Despite these limitations, the sensitivity analysis suggests that the results hold under different assumptions and scenarios.

An extension to this model would be to increase the timeframe of the model by making assumptions for outcomes beyond the clinical trial. For example, NP may be associated with higher costs in the long run, and some researchers have suggested that hospital stays are correlated with higher healthcare costs in the future.[23] By extending the model, QALY differences may be more pronounced, which will allow the outcomes to be expressed in cost/QALY terms in addition to ICPC. Some shortcomings of the current framework include the following: mortality rates in the two arms of the clinical trial were not statistically different, so the rates did not play a role in the analysis. If new data suggest different mortality rates, it may be a key driver in determining the cost effectiveness of linezolid. In addition, adverse events and treatment failure are assumed to only affect the length of stay in the hospital ward, which may be a simplistic generalization. Besides, there might be some overlap/double counting in hospital days due to adverse events, since these events also contributed to the total length of stay in the ZEPHyR study. Lastly, we leave it to future researchers to compare our results with other sources, such as prospective or retrospective datasets.

In summary, with better clinical response and less nephrotoxicity in the ZEPHyR study, first-line treatment of MRSA NP with linezolid was associated with higher drug costs and lower hospital costs in Taiwan, compared to vancomycin treatment. Depending on the cost-effectiveness threshold, linezolid may be a cost-effective treatment strategy for MRSA NP in Taiwan.

Conflicts of interest

Acknowledgments

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