Cost-Effectiveness Analysis of the Treatment of Ventilator-Associated Pneumonia with Linezolid or Vancomycin in Spain

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Summary

The aim of this study was to assess the cost-effectiveness of linezolid (LIN) versus vancomycin (VAN) for the treatment of ventilator-associated pneumonia (VAP) using a decision model analysis from the National Health System perspective. Patients and participants comprising four subgroups were analyzed: all, Gram-positive (GP), *Staphylococcus aureus* (SA), methicillin-resistant SA (MRSA). The treatments were LIN 600 mg i.v., every 12 hours, 10 days and VAN 1,000 mg i.v., every 12 hours 10 days. The primary outcome was the incremental cost-effectiveness of LIN in terms of cost per added quality-adjusted life year (QALY) gained. The secondary outcome was the marginal cost per year of life saved (LYS) generated by using LIN. Clinical cure and survival rates estimates were derived from a retrospective analysis of two trials comparing LIN with VAN. QALY was based on time-trade off study. Resource use and unit costs (€2003) were obtained from Spanish VAP treatment and health cost databases. The additional QALY and LYS per LIN patients were 0.392; 0.688; 0.606; 1.805 and 0.471; 0.829; 0.729; 2.175 respectively, compared with those of VAN in the patients with VAP (all, GP, SA, and MRSA, respectively). The additional costs for LYS with LIN, as compared to VAN were 1,501.31; 827.63; 955.13 and 289.51 €, respectively. The additional cost per QALY with LIN was 1,803.87; 997.25; 1,149.00 and 348.85 €, respectively. Conclusions: LIN was more cost-effective than VAN in the treatment of VAP in Spain, with an additional cost per QALY/LYS gained below the acceptable threshold in Spain of € 30,000 for new therapies.

Key words: **Linezolid, vancomycin, ventilator-associated pneumonia, cost-effectiveness, QALY, LYS.**

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the leading cause of hospital-acquired infection among the patients admitted to Intensive Care Units (ICU) [1,2]. It results in high morbidity and mortality, prolongs hospitalization and generates significant economic costs [3-5]. According to the results of the study on surveillance of hospital-acquired infection in ICU (ENVIN-ICU), carried out in Spain in 2001, including 5,045 patients admitted to 67 ICUs, 311 VAP were detected, which account for 44.8% of the controlled infections, with an incidence density of 16.1 VAP per 1000 days of assisted ventilation [2]. The mortality of the patients where one or more VAP were identified was 32.7% [2].

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The recommendations of several scientific societies for the diagnosis and treatment of VAP have recently been published. They propose that, after clinical suspicion of VAP is established and after samples from the lower respiratory tract are obtained, empirical antibiotic therapy should be immediately instituted, subsequently adjusting it to the results of the microbiological tests [6,7].

In the case of late VAP or where there are factors which can modify the primary endogenous flora (previous use of antibiotics, *diabetes mellitus*, liver cirrhosis) it is recommended to start the empirical treatment with antibiotic combinations (a beta-lactam with antipseudomonas activity combined with an aminoglycoside or a quinolone) that can act against *Pseudomonas aeruginosa* and *Staphylococcus aureus*, the most common pathogens in this clinical condition [2,7]. The coverage of methicillin-resistant *S. aureus* (MRSA) is reserved for ICUs where there is a high incidence of this multiresistant pathogen. In Spanish ICUs, MRSA resistance is around 35%, which means that its empirical coverage is increasing in recent years [2,8]

Until recently, glycopeptides, vancomycin (VAB) or teicoplanin have been used for the empirical treatment of VAP when the presence of MRSA is suspected. The launching of a new family of antibiotics, oxazolidinones, where the first representative, linezolid (LIN), is active against most multiresistant Grampositive cocci, has increased the therapeutic options in this indication [9].

In a retrospective analysis [10] of two randomized clinical trials [11,12] comparing the efficacy of LIN vs VAN for the treatment of patients with VAP, higher cure and survival rates were found in the group of patients treated with LIN. This antibiotic has a higher purchasing cost than glycopeptides but patients treated with LIN were less likely to die of VAP. Therefore, it has been proposed to perform this study to establish the cost-effectiveness of LIN as compared to VAN in the treatment of VAP in Spain.

MATERIALS AND METHODS

Pharmacoeconomic model

The study consisted of the application of a pharmacoeconomic model, defined as a theoretical scheme that enables to make simulations of complex health processes related to drugs and that is prepared, following a previously established protocol, through estimations obtained based on the data available or published on efficacy, toxicity, and costs of the compared options [13].

The model was based on a previously published pharmacoeconomic model [14]. It had the following general characteristics: retrospective design, since data of efficacy and costs previously obtained were used; it was modeled through a decision tree (*Figure 1*); it was deterministic, which means that it was assumed that the probabilities of the events of the decision tree would be fixed values; a basic case scenario was estimated (with the most probable data from among those available) and a sensitivity analysis was performed to verify its stability. The main premises and estimations considered in the model are summarized in *Table 1*. The following softwares were used: Microsoft® Excel 2000 and DATA® 3.5 for Healthcare of TreeAge Software.

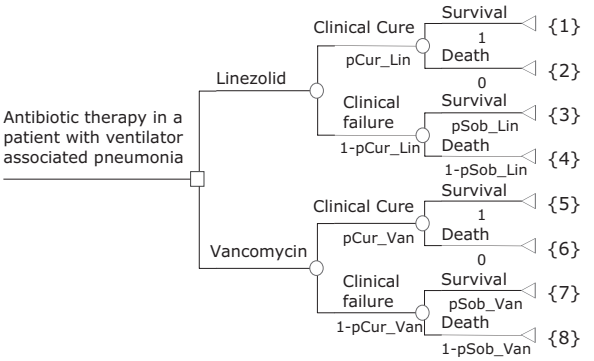

FIGURE 1 - Pharmacoeconomic model of the treatment of ventilator-associated pneumonia (VAP) with linezolid (LIN) or with vancomycin (VAN). pCur_Lin: probability of cure with LIN; pCur_Van: probability of cure with VAN; pSob_Lin: probability of outliving VAP with LIN treatment; pSob_Van: probability of outliving VAP with the treatment with VAN.

Estimation of efficacy, type of patients and type of analysis

All efficacy data were taken from the above mentioned retrospective analysis,[10] which combined the results of two double-blind, randomized, comparative clinical trials with LIN (600 mg i.v. every 12 hours) vs VAN (1,000 mg i.v. every 12 hours) in patients with VAP [11,12]. Specifically, four patient subgroups were studied: a) all those diagnosed with VAP (all), b) VAP due to Gram-positive organisms, c) VAP due to *Staphylococcus aureus* (SA) and d) VAP due to methicillin-resistant SA (MRSA).[10] As in the pharmacoeconomic analysis by Shorr *et al.*, in this study the estimated mean duration of the antibiotic therapies was 10 days (*Table 1*) [14].

The type of pharmacoeconomic analysis that should be applied depends on the existence or not of proven efficacy differences between the treatments. For that purpose, three efficacy criteria were considered: clinical cure, life-years saved (LYS) and quality-adjusted life years (QALY) [14].

The clinical cure rates were those shown in the follow-up visit (12-28 days after the end of the treatment), considering as "cure" the resolution of the

TABLE 1 - *Main premises and estimations considered in the pharmacoeconomic model of the treatment of ventilator-associated pneumonia (VAP) with linezolid (LIN) or vancomycin (VAN).*

Item	Premises and estimations		Sources
	LIN	**VAN**	
1. Antibiotic dose	600 mg every 12 h	1,000 mg every 12 h	6,8-10
2. Duration of the antibiotic treatment	10 days	10 days	6,8
3. Clinical cure rate (CI95%)			
All the patients with VAP (n=282)	45.4% (38.9; 51.9%)	36.7% (30.1; 43.3%)	6
VAP by Gram-positive (n=134)	53.7% (44.3; 63.1%)	37.7% (28.5; 46.9%)	6 6
VAP by *S. aureus* (n=110)	48.9% (38.5; 59.3%)	35.2% (25.4; 45.0%)	
VAP by MRSA (n=44)	62.2% (46.6; 77.8%)	21.2% (7.3; 35.1%)	6
4. Survival rate (CI95%)			
All the patients with VAP (n=262)	79.1% (74.4; 83.8%)	73.7% (68.4; 79.0%)	6
VAP by Gram-positive (n=130)	80.6% (73.9; 87.3%)	70.8% (63.0; 78.6%)	6
VAP by *S. aureus* (n=111)	78.2% (70.5; 85.9%)	70.3% (61.8; 78.8%)	6
VAP by MRSA (n=47)	84.1% (73.3; 94.9%)	61.7% (47.8; 75.6%)	6
5. Patients with VAN monitoring (minmax)	0%	10% (0-10%)	18
6. Life expectancy of patients with VAP	9 years	9 years	8,11
7. QALY per every year of survival after VAP (min-max)	0.83 (0.65-0.92)	0.83 (0.65-0.92)	8,12
8. Cost and benefit discount	No	No	16
9. Days of ICU stay (95%CI)	11.2 (10.2; 12.2)	11.4 (10.0; 12.8)	6
10. Resources in clinical failure	1 abdominothoracic CAT	1 abdominothoracic CAT	1,3
	1 bronchial brushing with telescoped catheter	1 bronchial brushing with telescoped catheter	
	1 Gram staining	1 Gram staining	
	1 bronchial aspirate culture	1 bronchial aspirate culture	

95%CI: confidence interval of 95%; max: maximum; min: minimum; n: number of patients; MRSA: methicillin-resistant *Staphylococcus aureus*; CAT: computerized axial tomography; ICU: intensive care unit.

signs and symptoms of pneumonia, with improvement or absence of worsening of the radiological findings [11,12].

The hospital survival rates were analyzed through the scores obtained with the severity scale "Acute Physiology and Chronic Health Evaluation II" (APACHE II) [15]. It was estimated that a 62-year old patient (mean age of the patients of the clinical trials analyzed) would have a life expectancy of 18 years. However, according to the study by Qartin *et al.*,[16] the survivors of a serious septic condition had their life expectancy reduced by 50%, which is the reason why it was assumed that life expectancy (LYS) after VAP would be 9 years [14].

Based on time-trade off questions, Hamel *et al* [17] concluded that survivors from an acute respiratory failure requiring assisted ventilation, the quality of life for each LYS was reduced by 8%. That is, if the value of the death and the perfect health during a year was 0 and 1 QALY, respectively, each year of survival with assisted ventilation would be equivalent to 0.92 QALY. However (as in the model of Shorr *et al*. [14]) a conservative assumption was made, adjusting that value to 10%, which means that in the analysis it was finally considered that a year with assisted ventilation would be equivalent to 0.83 QALY [14] (*Table 1*).

The cure and survival rates obtained with LIN were higher than with VAN in all cases (*Table 1*). Accordingly, a cost-effectiveness analysis (additional cost by LYS gained) was made. For this, the general guidelines for performing pharmacoeconomic analyses in Spain,[18] and the guidelines published by the Canadian Office of Coordination of the Assessment of Health Technologies [19] and Good Modeling Practice principles of the *International Society for Pharmacoeconomics and Outcomes Research* were followed [20].

Perspective of the analysis

In Spain, the medicinal products containing LIN and VAN are for hospital use and diagnosis, respectively. The study was conducted from the perspective of the National Health System (SNS) taking into account only direct health costs [14].

Time horizon

The time horizon of the model was adjusted to the duration of the treatment and to the time of follow-up of the patients required for the evaluation of the efficacy of the antibiotics administered in clinical trials: [10-12] the treatment of VAP had an approximate mean duration of 10 days in both groups; the confirmation of clinical cure was made in a consultation made between days 12 to 28 post-treatment; finally, as above discussed, the survival of patients who outlived VAP was estimated to be 50% of life expectancy at the age of 62 years (9 years) [14]. No cost (or benefit) discount was carried out, because only the costs incurred during the treatment of VAP were considered [21].

Decision-tree and estimation of probabilities

The decision tree attempts to represent as accurately as possible the events and the consequences occurring during the disease.

The tree of VAP used in this study is identical to that used by Shorr *et al.* [14] (*Figure 1*). The probabilities assigned to the tree (mean values and 95% CI) were estimated based on the results of the clinical trials (*Table 1*).

Cost estimation

The estimation of the costs of a disease treated with a given drug is made through the identification and quantification of the health resources involved and assigning to them some unit costs. Thus, the mean costs were estimated for a standard patient with VAP receiving treatment with LIN or VAN. The costs of the health resources used in the basic case of the model are expressed in Euros (€) of the year 2003 [21].

The use of resources in VAP was estimated mainly from two Spanish clinical practice guides in VAP [6,7] and from comparative clinical trials [10-12] (*Table 1*). The purchasing values of the antibiotic treatments were assessed (as laboratory sale prices from the drug database of the General Council of Colleges of Pharmacists [22]), the costs of monitoring VAN serum concentrations (that would occur in 10% of the patients, on the basis of a retrospective study by Abbot *et al* [23]), the costs of the diagnostic tests due to the clinical failure with LIN or VAN (1 abdominothoracic CAT, 1 bronchial brushing with telescoped catheter for sampling, 1 Gram staining and 1 quantitative culture of bronchial brushing) [6] and, finally, the costs derived from the days of stay at the ICU. In this regard, after the retrospective analysis of the clinical trials, minor differences favorable to LIN (a shorter stay) were seen,[10] that had economic impact (*Table 1*). The dosage regimens of the treatments considered in the model were those used in the clinical trial that, in turn, are those recommended in the SmPCs of the comparative antibiotics.

The unit costs of the health resources (VAN monitoring, diagnostic tests for clinical failure and stay in ICU) were obtained from a database of Spanish health costs (*Table 2*) [21].

Analysis of the decision tree

The decision tree (*Figure 1*) is analyzed through a method known as folding back analysis that starts in the terminal branches of the tree and consists of multiplying the costs (or the effects) by the probabilities of each branch and then sum the results of the branches stemming from the same knot, in order to obtain the value of the corresponding knot. This process continues from right to left, until a value is obtained for each alternative compared. With this model, the following analyses were made: an analysis of incremental costs (costs with LIN-costs with VAN), an incremental cost-effectiveness analysis (additional cost by LYS upon selecting the most effective option), and an incremental cost-utility analysis (the cost to gain a QALY, selecting the most effective option). The incremental cost-effectiveness and cost-utility analyses were made applying the following formula:

TABLE 2 - *Unit costs used in the pharmacoeconomic analysis of the treatment with linezolid or vancomycin in patients with ventilator-associated pneumonia.*

Resource (n., type)	Unit cost (Euros) *	Reference
Linezolid (10 injectables of 600 mg, LSP)	635.02	17
Vancomycin (1 injectable of 1,000 mg, LSP)	16.93 17.22 17.23	17 17 17
Vancomycin (100 injectables of 1,000 mg, LSP)	995.85	17
Monitoring of vancomycin levels (1)	24.82 (20.33-34.99)	21
Abdominothoracic CAT (1)	167.89 (29.74-263.48)	21
Bronchial brushing with telescoped catheter (1)	115.99 (29.42-191.70)	21
Gram staining (1)	3.82 (1.09-10.53)	21
Quantitative culture of bronchial brushing (1)	33.73 (7.83-33.73)	21
Day of ICU stay (1)	1,155.14 (745.80-1,722.37)	21

* In brackets, the minimum and maximum values of each cost.
LSP: laboratory sale price; CAT: computerized axial tomography; ICU: intensive care unit.

$$\frac{\text{Costs with LIN-Costs with VAN}}{\text{Effectiveness or utility with LIN - Effectiveness or utility with VAN}}$$

Basic case and analysis of sensitivity

In the basic case of the study, the mean values and the above-mentioned assumptions, summarized in *Table 1,* were considered.

In order to verify the stability of the results of the basic case and the ruggedness of the estimations made, several simple univariate analyses of sensitivity (a single variable is modified in each analysis) were made considering the worst and the best scenario for LIN and the minimum and maximum cure and survival values (estimates from 95% CI). The worst scenario for LIN consisted of the following assumptions: (i) the lower purchasing cost of VAN; (ii) that there would not be costs of monitoring VAN serum levels; (iii) that there would be no additional costs for the prolongation of ICU stay in patients treated with VAN; and, finally, (iv) the lowest probabilities of cure and survival with LIN and the highest with VAN (minimum and maximum values of the corresponding 95% CI). The other extreme case (the best scenario for LIN) consisted of assuming the assumptions contrary to those indicated for the previous scenario.

RESULTS

Of the 1,030 cases of nosocomial pneumonia included in the two clinical trials on which this study was based, 544 (52.8%) were VAP. In 282 (51.8%) cases, the treatment was carried out with LIN and in 262 (48.2%) with VAN. Of the cases treated with LIN, in 134 cases (47.5%) Gram-positive pathogens were identified, 110 of which were SA and 44 MRSA, while in those receiving VAN, 130 cases with Gram-positive pathogens (49.6%) were identified, of which 111 were SA and 47 MRSA [10].

No differences were seen in the main characteristics of the patients treated with LIN or VAN, including sex (man, 66.3% vs 65%), age (>65 years, 51.1% vs 44.7%), severity degree (APACHE II >20, 22.7% vs 21.5%), or need for AV (AV >7 days, 28.0% vs 31,3%) [10].

The results of the basic case and of the sensitivity analyses are shown in *Tables 3 to 6*. *Tables 3 and 5* refer to the additional costs per LYS or QALY gained, respectively, in all cases of VAP and in VAP due to Gram-positive pathogens. *Tables 4*

TABLE 3 - *Results of the cost-effectiveness analysis (cost by LYS) of the treatment of ventilator-associated pneumonia (VAP) with linezolid (LIN) or vancomycin (VAN). All VAP and those due to Gram-positive organisms.*

SCENARIO	COSTS (€)			EFFICACY (LYS)			INCREMENTAL
	LIN	VAN	dif	LIN	VAN	dif	COST-EFFECTIVENESS (€)[1]
All VAP							
Basic case	1,453.79	746.67	707.12	7.973	7.502	0.471	1,501.31
Worst scenario for LIN[2]	1,311.64	254.78	1,056.86	7.529	7.928	-0.279	VAN dominates[4]
Best scenario for LIN[3]	1,510.27	1,502.16	8.11	8.299	7.012	1.287	6,30
Minimum cure and survival v.	1,475.66	756.31	719.35	7.592	7.012	0.580	1.240.26
Maximum cure and survival v.	1,431.91	735.41	696.50	8.299	7.928	0.371	1.877.36
VAP due to Gram-positive pathogens							
Basic case	1,425.85	739.74	686.11	8.192	7.363	0.829	827.63
Worst scenario for LIN[2]	1,307.96	251.25	1,056.71	7.692	7.977	-0.285	VAN dominates[4]
Best scenario for LIN[3]	1,454.33	1,465.03	-10.7	8.578	6.619	1.959	LIN dominates[4]
Minimum cure and survival v.	1,475.49	751.61	723.88	7.692	6.619	1.073	674.63
Maximum curve and survival v.	1,394.22	724.55	669.67	8.578	7.977	0.601	1,114.26

Other abbreviations: LYS: life-years saved; dif: difference.

[1] Cost difference/ efficacy difference (cost of an LYS, obtained with the most effective alternative).

[2] Considering the lower purchasing cost of VAN, that there would be no costs from VAN monitoring, that there would be no additional costs for prolongation of ICU stay in those treated with VAN, and also the lower probabilities of cure and of survival with LIN and the higher with VAN.

[3] Considering the assumptions contrary to those shown in the previous scenario.

[4] A treatment dominates another when it is more effective, with lower costs.

TABLE 4 - *Results of the cost-effectiveness analysis (cost for LYS) of the treatment of ventilator-associated pneumonia (VAP) with linezolid (LIN) or vancomycin (VAN). VAP due to S. aureus and methcillin-resistant S. aureus (MRSA).*

SCENARIO	COSTS (€)			EFFICACY (LYS)			INCREMENTAL
	LIN	VAN	dif	LIN	VAN	dif	COST-EFFECTIVENESS (€)[1]
VAP due to *S. aureus*							
Basic case	1,442.01	745.72	696.29	7.997	7.268	0.729	955.13
Worst scenario for LIN[2]	1,311.91	253.11	1,058.80	7.367	7.951	-0.584	VAN dominates[4]
Best scenario for LIN[3]	1,473.31	1,459.41	13.90	8.484	6.435	2.049	6.78
Minimum cure and survival v.	1,477.01	757.32	719.69	7.367	6.435	0.932	772.20
Maximum cure and survival v.	1,407.01	730.26	676.75	8.484	7.951	0.533	1,269.70
VAP due to MRSA							
Basic case	1,397.25	767.57	629.68	8.459	6.284	2.175	289.51
Worst scenario for LIN[2]	1,306.39	262.82	1,043.57	7.717	7.575	0.142	7,349.08
Best scenario for LIN[3]	1,380.92	1,344.24	36.68	8.898	4.645	4.253	8.62
Minimum cure and survival v.	1,449.75	772.28	677.47	7.717	4.645	3.072	220.53
Maximum cure and survival v.	1,344.75	753.93	590.82	8.898	7.575	1.323	446.57

Other abbreviations: LYS: life-years saved; dif: difference.

[1] Cost difference/ efficacy difference (cost of a LYS, obtained with the most effective alternative).

[2] Considering the lower purchasing cost of VAN, that there would be no costs from VAN monitoring, that there would be no additional costs for prolongation of ICU stay in those treated with VAN, and the lower probabilities of cure and of survival with LIN and the higher with VAN.

[3] Considering the assumptions contrary to those shown in the previous scenario.

[4] A treatment dominates another when it is more effective, with lower costs.

TABLE 5 - *Results of the cost-effectiveness analysis (cost for QALY) of the treatment of ventilator-associated pneumonia (VAP) with linezolid (LIN) or vancomycin (VAN). All VAP and due to Gram-positive organisms.*

SCENARIO	COSTS (€)			EFFICACY (AVAC)			INCREMENTAL
	LIN	VAN	dif	LIN	VAN	dif	COST-EFFECTIVENESS (€)[1]
All VAP							
Basic case	1,453.79	746.67	707.12	6.618	6.226	0.392	1,803.87
Worst scenario for LIN[2]	1,311.64	254.78	1,056.86	6.302	6.581	-0.279	VAN dominates[4]
Best scenario for LIN[3]	1,510.27	1,502.16	8.11	6.888	5.820	1.068	7.59
Minimum cure and survival v.	1,475.66	756.31	719.35	6.302	5.820	0.482	1,492.43
Maximum cure and survival v.	1,431.91	735.41	696.50	6.888	6.581	0.307	2,268.73
VAP due to Gram-positive pathogens							
Basic case	1,425.85	739.74	686.11	6.799	6.111	0.688	997.25
Worst scenario for LIN[2]	1,307.96	251.25	1,056.71	6.384	6.621	-0.237	VAN dominates[4]
Best scenario for LIN[3]	1,454.33	1,465.03	-10.7	7.120	5.494	1.626	LIN dominates[4]
Minimum cure and survival v.	1,475.49	751.61	723.88	6.384	5.494	0.890	813.35
Maximum cure and survival v.	1,394.22	724.55	669.67	7.120	6.621	0.499	1,342.02

Other abbreviations: LYS: life-years saved; dif: difference.

[1] Cost difference/ efficacy difference (cost of a LYS, obtained with the most effective alternative).

[2] Considering the lower purchasing cost of VAN, that there would be no costs from VAN monitoring, that there would be no additional costs for prolongation of ICU stay in those treated with VAN, and the lower probabilities of cure and of survival with LIN and the higher with VAN.

[3] Considering the assumptions contrary to those shown in the previous scenario.

[4] A treatment dominates another when it is more effective, with lower costs.

TABLE 6 - *Results of the cost-effectiveness analysis (cost for QALY) of the treatment of ventilator-associated pneumonia (VAP) with linezolid (LIN) or vancomycin (VAN). VAP due to S. aureus and methicillin-resistant S. aureus (MRSA).*

SCENARIO	COSTS (€)			EFFICACY (AVAC)			INCREMENTAL
	LIN	VAN	dif	LIN	VAN	dif	COST-EFFECTIVENESS (€)[1]
VAP due to *S. aureus*							
Basic case	1,442.01	745.72	696.29	6.638	6.032	0.606	1,149.00
Worst scenario for LIN[2]	1,311.91	253.11	1,058.80	6.115	6.599	-0.484	VAN dominates[4]
Best scenario for LIN[3]	1,473.31	1,459.41	13.90	7.041	5.341	1.700	8.17
Minimum cure and survival v.	1,477.01	757.32	719.69	6.115	5.341	0.774	929.83
Maximum cure and survival v.	1,407.01	730.26	676.75	7.041	6.599	0.442	1,531.11
VAP due to MRSA							
Basic case	1,397.25	767.57	629.68	7.021	5.216	1.805	348.85
Worst scenario for LIN[2]	1,306.39	262.82	1,043.57	6.405	6.287	0.118	8,843.81
Best scenario for LIN[3]	1,380.92	1,344.24	36.68	7.385	3.855	3.530	10.39
Minimum cure and survival v.	1,449.75	772.28	677.47	6.405	3.855	2.550	265.67
Maximum cure and survival v.	1,344.75	753.93	590.82	7.385	6.287	1.098	538.08

Other abbreviations: LYS: life-years saved; dif: difference.

[1] Cost difference/ efficacy difference (cost of an LYS, obtained with the most effective alternative).

[2] Considering the lower purchasing cost of VAN, that there would be no costs from VAN monitoring, that there would be no additional costs for prolongation of ICU stay in those treated with VAN, and the lower probabilities of cure and of survival with LIN and the higher with VAN.

[3] Considering the assumptions contrary to those shown in the previous scenario.

[4] A treatment dominates another when it is more effective, with lower costs.

and 6 show the additional costs for LYS or QALY gained, respectively, in VAP due to SA and due to MRSA.

Basic case

The treatment with LIN was more effective that VAN, providing more LYS (0.471; 0.829; 0.729 and 2.175) and more QALY (0.392; 0.688; 0.606 and 1.805) in patients with VAP (all, Gram-positive pathogens, SA and MRSA, respectively). Due to its higher purchasing cost, LIN also generated more costs that VAN (707.12; 686.11; 696.29 and 629.68 €, respectively). Accordingly, the additional cost per LYS with LIN, as compared to VAN, was 1,501.31; 827.63; 955.13 and 289.51 €, respectively. The additional cost for QALY gained with LIN was 1,803.87; 997.25; 1,149.00 and 348.85 €, respectively.

Sensitivity analysis

The basic case was stable for the minimum and maximum efficacy values and sensitive to the analysis of extreme (and improbable) scenarios: in the worst scenario for LIN, VAN was the dominant alternative (more effective and less costly than LIN) in all cases, except for MRSA. On the contrary, LIN was dominant in the most favorable assumption in the patients with VAP due to Gram-positive pathogens.

DISCUSSION

According to the results of this model, LIN is a more effective antibiotic therapy for VAP than VAN (with higher cure and survival rates), but it is also more costly, due its higher acquisition cost. The incremental cost for LYS or for QALY when LIN is used, ranges, in the basic case, from 300 to 1,800 €, approximately. This cost of obtaining an LYS or an additional QALY would be much lower than the maximum cost (about 30,000 €) that would be considered assumable in Spain [25].

Weaknesses and strengths of the model

In the evaluation of these results, a number of limitations and strengths of the study should be considered. First, it is a theoretical model (which is, by definition, a simplified simulation of reality) based on the results of non-pragmatic clinical trials. However, the clinical trials directly compared the treatments, so no indirect efficacy comparisons should be made. Second, the use of resources was estimated retrospectively from Spanish guides on clinical actuation (that would reflect the clinical practice in our country) and on the clinical trials themselves (that would give internal validity to the estimations). Finally, several sensitivity analyses were performed, which confirmed the stability of the results of the basic case, except for the analyses of the most extreme and improbable scenarios.

Agreement with other analyses

It is of interest to verify the results obtained in this study with those of the study by Shorr *et al.* [14] on which the model developed in this paper was based. When applied to the United States, the incremental cost per LYS or additional QALY in patients with VAP for SA treated with LIN (to which the simulation was limited) was US$22,072 and US$29,945, respectively [14]. That is, though the absolute cost would be higher than in the Spanish model (possibly due, among other reasons, to the differences in the health costs and to the fact that in the US study long-term costs were also considered) LIN would still be cost-effective according to the parameters applicable in Spain [25].

Clinical assessment

One of the limitations of the model applied is based on the very low possibility that the worst scenario for LIN is reproducible in daily clinical practice. The critical patients with assisted ventilation treated with VAN frequently undergo dose adjustments through the monitoring of plasma levels, so the assumption including ruling out the costs derived from this technique is improbable. In addition, all the clinical trials comparing LIN to VAN have shown a shorter duration of treatment and higher clinical response and survival rates in the group of patients treated with LIN [11,12,26]. Furthermore, in the best of the scenarios for LIN the costs derived from toxicity related to treatment with VAN were not considered.

The results of this model indicate that a higher purchasing cost does not necessarily mean that a treatment is not cost-effective. According to the results of the comparative clinical trials with LIN and VAN, the former would provide higher cure and survival rates in patients with VAP, with additional costs possibly assumable by the Spanish National Health System.

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