Eur J Clin Microbiol Infect Dis (2011) 30:635–643
DOI 10.1007/s10096-010-1133-6

ARTICLE

Impact of administration of vancomycin or linezolid to critically ill patients with impaired renal function

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Received: 23 June 2010 / Accepted: 17 December 2010 / Published online: 12 January 2011
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Abstract The aim of this study was to assess the impact of vancomycin (VAN) versus linezolid (LZD) on renal function in patients with renal failure (RF) admitted to intensive care units. This was a multicenter, retrospective, comparative cohort study. Renal failure patients were treated with VAN or LZD for proven or suspected infections by multiresistant Gram-positive cocci. Changes in plasma creatinine levels and creatinine clearance at the start and end of treatment were used as endpoints. A total of 147 patients were treated with VAN (group A, n=68) or LZD (group B, n=79). Group B included more patients with diabetes mellitus [9 (13.2%) vs. 25 (31.6%); p = 0.007], septic shock [39 (57.4%) vs. 60 (75.9%); p = 0.013] and greater RF (mean ClCr 42.24 ml/min vs. 37.57 ml/min; p = 0.04). Renal function improved in patients from both groups who did not require renal replacement therapy. A greater improvement was seen in group B [percent decrease in Cr (27.94 vs. 9.48; p = 0.02) and percent increase in ClCr (95.96 vs. 55.06; p = 0.05)]. In group A, nine patients (13.2%) experienced an antibiotic-related increase in RF, and antibiotic was discontinued in five patients due to adverse effects. It is reasonable to avoid use of VAN in critically ill patients with acute renal failure.

The results of this study have previously been reported to the 44th National Congress of the Spanish Society of Intensive and Critical Medicine and Coronary Units (SEMICYUC), held in Valladolid on June 2009.

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Introduction

Multiple epidemiological studies, including those conducted at intensive care units (ICUs), show a significant increase in infections caused by Gram-positive cocci (GPCs), including their multiresistant strains (MR-GPCs) [1–6]. In Spain, according to data from the National Study of Nosocomial Infection Surveillance (ENVIN), the presence of methicillin-resistant *Staphylococcus aureus* in ICU-acquired infections has gradually increased, and accounted in 2006 for 4.6% of all isolates from ICU-acquired infections [2]. This proportion decreased in 2008 to 2.22%, or 25% of all *Staphylococcus aureus* (SA) identified [2]. On the other hand, resistance of coagulase-negative staphylococci (CNS) to methicillin continues to be higher than 80%. This epidemiological situation has led to an increased use of antibiotics active against these organisms, such as vancomycin (VAN) [7, 8] and linezolid (LZD). Tigecycline, a drug of the glycylcycline class, and daptomycin, a macrocyclic lipopeptide, have recently been added to this group of drugs. VAN and

LZD are the drugs most commonly used for critically ill patients, despite the fact that use of VAN is greatly controversial [9–15]. In addition to tolerability and renal toxicity problems, a high treatment failure rate in severe infections has been reported for VAN, probably related to its poor tissue penetration in the lung, bone tissue, central nervous system (CNS), and inflammatory fluids [16–20]. This requires use of higher doses, with the resultant increase in adverse events, one of the most significant of which is renal function impairment [21–26]. Despite these limitations, this glycopeptide continues to be widely used at Spanish ICUs. The possibility of monitoring VAN plasma levels and adjusting its dosage based on creatinine clearance has probably promoted use of the drug. However, the clinical impact of this decision is not known, and this study was therefore intended to assess the temporal changes in renal function in patients with biological criteria of renal failure (RF) treated with VAN versus LZD for documented or suspected infections by MR-GPCs.

Materials and methods

A multicenter, retrospective, observational study was conducted in 17 Spanish ICUs. Data from patients admitted to the participating ICUs in 2006 were retrospectively collected.

All patients over 18 years of age admitted to an ICU who were administered VAN or LZD (initially or as rescue treatment), alone or combined with other antimicrobial drugs, for proven or suspected infections by MR-GPCs in any site and who had renal impairment and were not subject to hemodialysis or any other renal replacement therapy (RRT) before or at the start of treatment were enrolled in the study. RF was defined as serum creatinine (Cr) levels higher than 1.5 mg/dL and/or Cr clearance (ClCr)<60 ml/min, as estimated using the Cockcroft-Gault equation [27].

Exclusion criteria included age under 18 years, use of VAN or LZD as prophylaxis, use of any RRT before or at treatment start, absence of renal function monitoring procedures, use of VAN or LZD for less than 3 days, and use of teicoplanin as initial treatment.

A comparative analysis was made of the groups of patients treated with VAN (group A) and with LZD (group B). Data collected included demographic characteristics, comorbidities, immunocompetence, ICU and hospital stay, mortality, reason for admission, infection site and microorganisms involved, type of treatment (empirical or specific), and reasons for treatment discontinuation. Infection severity was assessed both at admission and treatment start (APACHE II) [28], and infection was classified as sepsis, severe sepsis, and septic shock based on the criteria of Bone [29]. Cr and glomerular filtration rate (GFR) values, dosage used, and concomitant nephrotoxic medication (amikacin, tobramycin, gentamicin, colistin, acyclovir, tacrolimus, cyclosporine, and foscarnet) were also recorded during treatment. In VAN-treated patients, administration form (continuous or intermittent) and plasma levels of the drug (when measured) were recorded. Finally, RRTs performed during treatment were recorded, as well as their adverse effects and therapeutic result. An effectiveness analysis was performed on the complete intention-to-treat (ITT) sample and on the clinically evaluable population (CEP), defined as patients with a documented diagnosis of GPC infection.

Immunosuppressed patients were defined as those administered corticosteroid therapy (methylprednisolone> 40 mg/day for longer than 15 days) and/or treated with other immunosuppressants.

SA and CNS resistant to methicillin and/or VAN and VAN-resistant enterococci were considered as MR-GPCs. Clinical cure was defined as resolution of infection with no presence of signs or symptoms associated with the original infection, and microbiological eradication as complete eradication of the initial microorganisms. Treatment for at least three days was required to assess treatment failure.

To assess the impact of antibiotic therapy on renal function, patients not requiring any RRT during or within one week of therapy were analyzed. Patients who required RRT were separately analyzed. Plasma Cr levels and GFR were compared at both treatment start and end, and percent change in Cr and GFR was compared during treatment. This percentage was obtained using the following formula: (Cr at treatment end) – (Cr at treatment start) / (Cr at treatment start). Percent change in GFR was estimated using the same formula.

Statistical analysis

To assess differences in variables analyzed in both study arms, distribution of tested parameters was compared between the treatment groups using a Chi-square test for homogeneity of proportions in qualitative variables, and a Student's t test for independent quantitative variables. A value of p <0.05 was considered statistically significant. The nominal significance level was not adjusted for multiplicity.

Results

A total of 147 patients treated with VAN (n=68, group A) or LZD (n=79, group B) for documented or suspected

infections by MR-GPCs were enrolled in the study. Mean age of patients analyzed was 64 years (SD 13.98), and 70.7% were males. Mean APACHE II on admission was 21.71 (SD 7.36). Of all patients, 67.1% came from other hospital departments and 64.6% were medical patients. Sepsis was the most common reason for ICU admission (33.8%). ICU mortality was high, and hospital mortality was 50.3%. Table 1 shows the demographic characteristics, severity, admission diagnosis, and concomitant diseases of patients by treatment received. There were no significant differences between both groups. Concomitant diseases included chronic obstructive pulmonary disease and diabetes mellitus, which was more common in group B ($p = 0.007$).

Table 2 breaks down infections by type, location, and systemic response. Nosocomial infections were most common, accounting for 73% of all infections, with no differences between both treatment groups. Infections were quite serious, as shown by a mean APACHE II score of 21.88 points (SD 17.29) at the start of treatment. Septic shock occurred in 67.3% of all patients and in a greater percentage of patients given LZD ($p = 0.013$), while a higher proportion of sepsis with no organ failure was found in VAN-treated patients ($p = 0.002$).

One or more Gram-positive bacteria were isolated in 97 patients (65.9%). SA (40.2%) and CNS (32.9%) were the most commonly found microorganisms (Table 3). Polymicrobial infections associated to Gram-negative

Table 1 Demographic and clinical characteristics and concomitant diseases of patients by treatment group

Characteristics	Total (n=147)	VAN (n=68, Group A)	LZD (n=79, Group B)	p
Mean age (SD)	64.07 (13.98)	65.06 (14.64)	63.22 (13.41)	0.42
Male, n (%)	104 (70.7)	45 (66.2)	49 (74.7)	0.17
Mean APACHE II (SD)	21.71 (7.36)	21.83 (7.20)	21.62 (7.54)	0.86
Death at ICU, n (%)	57 (38.8)	27 (39.7)	30 (38.0)	0.48
Death at hospital, n (%)	74 (50.3)	38 (55.9)	36 (45.6)	0.14
Patient source, n (%)				
Community	44 (30.1)	22 (32.4)	22 (28.2)	
Hospital	98 (67.1)	43 (63.2)	55 (70.5)	0.40
Long-term facility	4 (2.7)	3 (4.4)	1 (0.7)	
Patient type, n (%)				
Medical	95 (64.6)	47 (69.1)	48 (60.8)	
Surgical	38 (25.9)	13 (19.1)	25 (31.6)	
Trauma	10 (6.8)	6 (8.8)	4 (5.1)	
Coronary	4 (2.7)	2 (2.9)	2 (2.5)	
Admission diagnosis, n (%)				
Cardiovascular disease	15 (10.3)	9 (13.2)	6 (7.8)	
Sepsis	49 (33.8)	24 (35.3)	25 (32.5)	
Trauma	8 (5.5)	5 (7.4)	3 (3.9)	
Respiratory failure	11 (7.6)	3 (4.4)	8 (10.4)	
Pneumonia	19 (13.1)	9 (13.2)	10 (13.0)	0.95
Pancreatitis	5 (3.4)	1 (1.5)	4 (5.2)	
Peritonitis	8 (5.5)	2 (2.9)	6 (7.8)	
Postoperative	5 (3.4)	1 (1.5)	4 (5.2)	
CNS disease	12 (8.3)	8 (11.8)	4 (5.2)	
Other	13 (9.0)	6 (8.8)	7 (9.1)	
Concomitant diseases, n (%)				
Diabetes	34 (23.1)	9 (13.2)	25 (31.6)	0.007
Immunodeficiency	42 (28.6)	21 (30.9)	21 (26.6)	0.34
Chronic renal failure	21 (14.3)	8 (11.8)	13 (16.5)	0.28
COPD	34 (23.1)	19 (27.9)	15 (19.0)	0.13
Severe heart failure	15 (10.2)	10 (14.7)	5 (6.3)	0.08
Chronic liver disease	16 (10.9)	10 (14.7)	6 (7.6)	0.13
Alcoholism	20 (13.6)	10 (14.7)	10 (12.7)	0.45

VAN vancomycin, *LZD* linezolid, *SD* standard deviation, *CNS* central nervous system, *COPD* chronic obstructive pulmonary disease

Table 2 Infection type, location, and severity by treatment group

Infection type, *n* (%)	Total (*n*=147)	VAN (*n*=68, Group A)	LZD (*n*=79, Group B)	*p*
Community-acquired	39 (26.5)	19 (27.9)	20 (25.3)	
Hospital-acquired (outside ICU)	55 (37.4)	25 (36.8)	30 (38.0)	0.93
ICU-acquired	53 (36.1)	24 (35.3)	29 (36.7)	
Location, *n* (%)				
VAP	18 (12.2)	9 (13.2)	9 (11.4)	
Primary bacteremia	17 (11.6)	8 (11.8)	9 (11.4)	
Secondary bacteremia	16 (10.9)	9 (13.2)	7 (8.9)	
Vascular catheter infection	14 (9.5)	8 (11.8)	6 (7.6)	
Non-VAP	34 (23.1)	13 (19.1)	21 (26.6)	0.67
Non-CAUTI	3 (2.0)	2 (2.9)	1 (1.3)	
SWI	20 (13.6)	10 (14.7)	10 (12.7)	
SSTI	7 (4.8)	4 (5.9)	3 (3.8)	
Other locations	18 (12.2)	5 (7.4)	13 (16.5)	
Severity at treatment start				
Mean APACHE II (SD)	21.88 (7.29)	22.54 (7.87)	21.31 (6.75)	0.31
Sepsis *n* (%)	24 (16.3)	18 (26.5)	6 (7.6)	0.002
Severe sepsis, *n* (%)	24 (16.3)	11 (16.2)	13 (16.5)	0.57
Septic shock, *n* (%)	99 (67.3)	39 (57.4)	60 (75.9)	0.013

VAP ventilator-associated pneumonia, *non-VAP* non-ventilator-associated pneumonia, *non-CAUTI* non-catheter-associated urinary tract infection, *SSTI* skin and soft tissue infection, *SWI* surgical wound infection, *SD* standard deviation

bacilli were found in 24.7% of patients, with no difference between the two treatment groups analyzed (Table 3). VAN and LZD were administered in most cases empirically (76.2%) and combined with other antimicrobials, most commonly broad-spectrum antibiotics (87.1%). Combinations with piperacillin/tazobactam and carbapenems were most common. No differences were found between the groups compared. The duration of the treatment was longer in group B [11.27 (SD 8.98) vs. 7.44 days (SD 4.17); $p = 0.002$]. VAN was continuously administered to 15 patients (22.1%). Steady state plasma levels of VAN were measured in ten (66.7%) of these patients [mean 21.16 μg/ml (SD 6.56)]. In 18 (34%) of the 53 patients on intermittent administration, trough levels were measured [mean 29.26 μg/ml (SD 13.47)].

At treatment start, group B patients had a greater renal function impairment than group A patients, as shown by higher mean Cr levels (2.30 vs. 2.11) and significantly

Table 3 Microorganisms identified in infections included in the study

Microorganisms	Total (*n*=97)	VAN (*n*=44)	LZD (*n*=53)
Gram-positive, *n* (%)	97/147 (65.9)	44/97 (45.4)	53/97 (54.6)
Staphylococcus aureus, MS	17/97 (17.5)	7/44 (15.9)	10/53 (18.9)
Staphylococcus aureus, MR	22/97 (22.7)	6/44 (13.6)	16/53 (30.2)
Coagulase-negative *Staphylococcus*	32/97 (32.9)	13/44 (29.5)	19/53 (35.8)
Other staphylococci	2/97 (2.1)	1/44 (2.3)	1/53 (1.9)
Streptococcus pneumoniae	5/97 (5.2)	4/44 (9.1)	1/53 (1.9)
Enterococcus faecalis	4/97 (4.1)	4/44 (9.1)	0/53 (0.0)
Enterococcus faecium	8/97 (8.2)	5/44 (11.4)	3/53 (5.7)
Other streptococci	7/97 (7.2)	4/44 (9.1)	3/53 (5.7)
Associated to GNBs	24/97 (24.7)	11/24 (45.8)	13/24 (54.2)
Pseudomonas aeruginosa	6/24 (25)	4/11 (36.4)	2/13 (15.4)
Escherichia coli	4/24 (16.7)	2/11 (18.2)	2/13 (15.4)
Klebsiella pneumoniae	3/24 (12.5)	1/11 (9.1)	2/13 (15.4)
Other GNBs	7/24 (29.2)	3/11 (27.3)	4/13 (30.8)

GNBs Gram-negative bacilli

Table 4 General characteristics and change in renal function of patients undergoing RRT during antibiotic therapy

Parameter	Total (n=18)	VAN (n=4)	LZD (n=14)	p
Demographic characteristics and infection severity and presentation				
Mean age (SD)	65.28 (10.76)	69.00 (5.77)	64.21 (11.76)	0.45
Male, *n* (%)	14 (77.8)	3 (75)	11 (78.6)	0.88
Mean APACHE II (SD)	24.22 (7.53)	27.25 (9.91)	23.35 (6.92)	0.37
Severe sepsis, *n* (%)	3 (16.7)	1 (25)	2 (14.3)	0.61
Septic shock, *n* (%)	14 (77.8)	3 (75)	11 (78.6)	0.88
Death at ICU, *n* (%)	14 (77.8)	3 (75)	11 (78.6)	0.88
Concomitant diseases, *n* (%)				
Diabetes (%)	8 (44.4)	3 (75)	5 (35.7)	0.16
CRF (%)	6 (33.3)	1 (25)	5 (35.7)	0.68
COPD (%)	5 (27.8)	1 (25)	4 (28.6)	0.13
Change in renal function over time				
Creatinine at treatment start		3.52 (1.60)	3.36 (1.49)	0.85
Creatinine at treatment end		2.09 (0.79)	2.03 (1.40)	0.94
Percent change in creatinine		−13.68 (79.57)	-39.15 (30.11)	0.57
ClCr at treatment start		30.04 (20.93)	28.23 (12.65)	0.83
ClCr at treatment end		42.61 (14.98)	60.92 (47.99)	0.47
Percent change in ClCr		122.17 (194.66)	117.27 (137.22)	0.95

SD standard deviation, *RRT* renal replacement therapy, *Creat* creatinine, *ClCr* creatinine clearance, *CRF* chronic renal failure, *COPD* chronic obstructive pulmonary disease

Values given as mean (SD) unless otherwise noted

lower ClCr values (37.57 vs. 42.24, p = 0.04). During treatment, RRTs were used in 18/147 patients (12.2%). Continuous venovenous hemodiafiltration (CVVHDF) was the RRT used in 14 of these patients. Renal function support measures were used more frequently in group B [14/79 (17.7%)] as compared to group A [4/68 (5.9%)], and CVVHDF was indicated in most cases (12/14; 85.7%). Table 4 details demographic characteristics, severity, organic impact of infections, mortality, and renal function changes over time in these patients. Chronic renal failure was diagnosed in 33.3% (6/18) of the patients, and was more prevalent in group B (35.7% vs. 25%), even though the difference was not statistically significant. Mean APACHE II score was 24.22, 77.8% were in septic shock, and mortality was 77.8%. There were no significant differences between both groups of antibiotic therapy.

Concomitant nephrotoxic drugs were administered to 27.9% of patients, with no differences between both groups [17/68 (25%) vs. 24/79 (30.4%), p = 0.29]. Aminoglycosides were most common in both groups [11/17 (63.4%) vs. 15/24 (62.5%) p = 0.70].

Table 5 shows the changes in plasma Cr levels and GFR from the start to the end of treatment as measured in the 129 patients (85.8%) who required no extrarenal clearance techniques during or at the end of treatment. GFR improved during antibiotic therapy in both groups, with a resultant decrease in Cr levels, but a greater improvement was seen in LZD-treated patients (p = 0.05 and p = 0.02, respectively) (Fig. 1). Clinical and microbiological effectiveness was compared by ITT and in the CEP (Table 6); clinical cure rates were 49.7% and 67.0%, respectively. They were higher in group B in both cases, but the difference was not statistically significant. Microbiological eradication rates were 48.3% and 61.9%. Higher rates were found in group B, but there were more indeterminate results in group A.

Twelve (8.2%) adverse effects related to the antibiotics tested were recorded. Nine (13.2%) patients treated with

Table 5 Analysis of change in renal failure in patients undergoing no RRT during or at the end of antibiotic therapy

Patients (n=129)	VAN (n=64)	LZD (n=65)	p
Creatinine at treatment start	2.02 (1.91)	2.08 (0.91)	0.82
Creatinine at treatment end	1.65 (1.34)	1.40 (0.84)	0.20
Percent change in creatinine	−9.48 (51.92)	−27.94 (41.11)	0.02
ClCr at treatment start	43.01 (13.44)	39.58 (13.34)	0.14
ClCr at treatment end	63.57 (41.91)	75.80 (56.69)	0.16
Percent change in ClCr	55.06 (112.91)	95.96 (127.40)	0.05

VAN vancomycin, *LZD* linezolid, *SD* standard deviation, *RRT* renal replacement therapy, *ClCr* creatinine clearance

Values given as mean (SD)

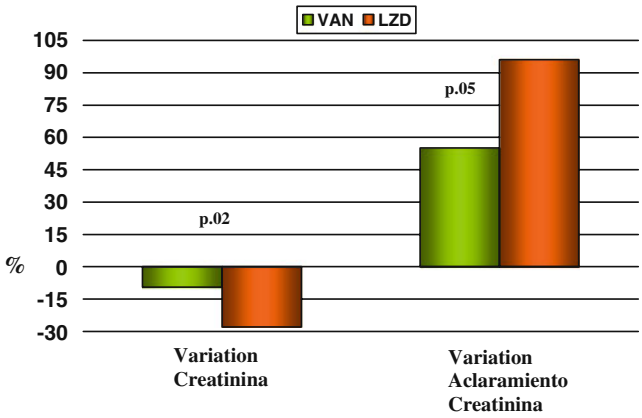

Fig. 1 Glomerular filtration rate (GFR) improvement with vancomycin (VAN) versus linezolid (LZD)

VAN had an increased renal impairment which was attributed to drug administration, as compared to none of the patients treated with LZD (p = 0.001). Thrombocytopenia occurred in three patients (3.8%) treated with LZD and in no patient in the VAN group (p = 0.15).

Table 7 shows the reasons for treatment discontinuation. The main reason for stopping treatment was clinical cure (49.7% of patients), which occurred in significantly more group B patients (55.7% vs. 42.6%, p = 0.04). Treatment was discontinued for adverse effects in five patients, all from group A (7.4% vs. 0.0%, p = 0.02).

Discussion

This observational, retrospective study to analyze the impact of use of VAN and LZD in patients with biological criteria of RF showed a better evolution of renal function in critically ill patients with documented or suspected infection by MR-GPCs when treated with LZD as compared to VAN. Although an overall improvement in renal function occurred in both groups, VAN-treated patients had a significantly lower improvement, and 13.2% of them experienced a worsening in renal function attributable to VAN which required drug discontinuation in half of them. It is currently recommended that VAN trough plasma levels ranging from 15 to 20 μg/ml are achieved, and even higher levels if infection involves the CNS [25, 26]. This requires use of doses up to 60 mg/kg/day, which involves a greater risk of renal toxicity. These recommendations have been supported by the results of recent studies showing that minimal inhibitory concentration (MIC) of VAN against SA has increased since the 1990s. There are studies reporting an incidence of strains with MIC>1 μg/ml higher than 50%, which is associated with a decreased therapeutic effectiveness [21–24]. In this setting, if VAN administration is decided, MICs of VAN against the pathogens involved would have to be known and VAN plasma levels would have to be monitored, mainly in critically ill patients with severe sepsis, in whom changes in hemodynamics and distribution volume are also common. In our study,

Table 6 Effectiveness

Intention-to-treat population	Total (n=147)	VAN (n=68; Group A)	LZD (n=79; Group B)	p
Clinical effectiveness				
Cure	73 (49.7)	29 (42.6)	44 (55.7)	0.11
Failure	33 (22.4)	20 (29.4)	13 (16.5)	
Indeterminate	41 (27.9)	19 (27.9)	22 (27.8)	
Microbiological effectiveness				
Eradication	71 (48.3)	26 (38.2)	45 (57.9)	0.04
Persistence	12 (8.2)	5 (7.4)	7 (8.9)	
Indeterminate	64 (43.5)	37 (54.4)	27 (34.2)	
Clinically evaluable population	Total (n=97)	VAN (n=44)	LZD (n=53)	p
Clinical effectiveness[a]				
Cure	65 (67.0)	26 (59.1)	39 (73.6)	0.23
Failure	25 (25.8)	15 (34.1)	10 (18.9)	
Indeterminate	7 (7.2)	3 (6.8)	4 (7.5)	
Microbiological effectiveness[a]				
Eradication	60 (61.9)	23 (52.3)	37 (69.8)	0.02
Persistence	8 (8.2)	2 (4.5)	6 (11.3)	
Indeterminate	29 (29.9)	19 (43.2)	10 (18.9)	

Values given as n (%)

[a] Documented diagnosis of GPC infection

Table 7 Reasons for treatment discontinuation

Reason for treatment discontinuation	Total (n=147)	VAN (n=68; Group A)	LZD (n=79; Group B)	p
Clinical cure	73 (49.7)	29 (42.6)	44 (55.7)	0.04
Clinical failure	33 (22.4)	20 (29.4)	13 (16.5)	0.07
Adverse effects	5 (3.4)	5 (7.4)	0 (0.0)	0.02
No GPC infection	15 (10.2)	8 (11.8)	7 (8.9)	0.37
Treatment downtitration	14 (9.5)	5 (7.4)	9 (11.4)	0.29
Indeterminate	7 (4.8)	1 (1.5)	6 (7.6)	0.08

VAN vancomycin, *LZD* linezolid

Values given as *n* (%)

reporting use of VAN in some Spanish ICUs in 2006, such levels were measured in few cases (in 66.7% and 34% of patients on continuous and intermittent administration, respectively), and mean values obtained were in the upper range of recommended concentrations (21.16 μg/ml and 29.26 μg/ml, respectively). These data support the convenience of monitoring VAN levels in these patients when the drug is used, and also the need to consider alternative treatment particularly in severe infections and when the MIC of this antibiotic against SA is unknown or higher than 1 μg/ml. While the proportion of patients on hemodialysis was similar in both groups, CVVHDF was used in 15.2% of patients treated with LZD as compared to 2.9% of patients treated with VAN (p = 0.01). It should be noted that patients treated with LZD had a greater renal function impairment at baseline, as shown by a lower ClCr at treatment start (37.57 vs. 42.24, p = 0.04). On the other hand, among group B patients undergoing RRTs, 35.7% had chronic renal failure, as compared to 25% in group A; although the difference was not statistically significant. Finally, it is very likely that the greater proportion of patients with septic shock in the group treated with LZD (75.9% LZD vs. 57.4% VAN, p = 0.013) and the fact that 11 out of the 14 patients in this group receiving RRT were in such hemodynamic situation (78.6%) influenced the higher rate of CVVHDF which, as known, is a procedure used to remove inflammatory mediators in the systemic inflammatory response syndrome of sepsis.

On the other hand, another aspect worthy of mentioning is the percentage of cases of thrombocytopenia related with the antibiotic treatment (3.8%), considering that it was higher than what would have been expected in patients treated with LZD, taken into account the duration of the treatment [11.27 days (SD 8.98)]. This result could also have been conditioned by a more serious presentation of the infection in this patient group.

ICU and hospital mortality of patients enrolled into this study was high. This was related to the severity of the condition of these patients, as shown by both mean APACHE II (21.88) and impact on organs of infections occurring as severe sepsis/septic shock in 83.6% of cases. It should be noted that while a greater systemic impact was seen in patients treated with LZD (75.9% vs. 57.4% patients in septic shock), there were no differences in mortality.

In the effectiveness analysis by IT and in the CEP, a higher cure rate was seen in LZD-treated patients, but the difference was not statistically significant, probably because of the small size of the sample used to analyze this variable. Analysis of microbiological effectiveness did not provide significant conclusions. Although microbiological eradication rates were significantly higher in group B, a significantly greater proportion of indeterminate results was found in group A. On the other hand, an analysis of the reasons for drug discontinuation showed superiority of LZD over VAN. Among LZD patients, there were more cases where treatment was discontinued due to clinical cure (55.7% vs. 42.6%, p = 0.04) and less patients with drug discontinuation for adverse effects (7.4% vs. 0%, p = 0.02). Both data show the higher effectiveness of LZD as compared to VAN for treating this group of patients with impaired renal function.

Limitations of this study include retrospective data collection, with its inherent limitations. Despite this important consideration, retrospective recruitment was consecutively performed, with a balanced number of patients in both treatment groups included at each hospital. Sample size was adequate for analyzing the primary objective of the study, and although the group treated with LZD included patients who were more seriously ill and, had lower ClCr values, and a greater proportion of patients with diabetes mellitus, this does not invalidate results because renal function evolved better in this group.

Based on the results of this study, it is reasonable to conclude that use of VAN should be avoided in critically ill patients with acute renal failure. If VAN is used, it is essential to monitor its plasma levels and to ascertain the MICs for the pathogens involved in infection.

Funding and conflict of interest statement This study was funded by an unrestricted educational research grant from Pfizer Spain (NRA5950008). F.A.L. received a grant from Gilead, honoraria as lecturer from Pfizer, Wyeth, Sanofi-Aventis, Gilead, MSD, and Novartis, and consultancy fees from Pfizer, Novartis, Wyeth, and Cephalon. O.R.C. received technical support for research from Wyeth Farma, honoraria as lecturer from Lilly and Pfizer, and consultancy fees from Pfizer.

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