MAJOR ARTICLE

Effect of Clarithromycin in Patients with Sepsis and Ventilator-Associated Pneumonia

Evangelos J. Giamarellos-Bourboulis,[1] Jean-Claude Pechère,[4] Christina Routsi,[2] Diamantis Plachouras,[1] Spyridon Kollias,[2] Maria Raftogiannis,[1] Dimitrios Zervakis,[2] Fotini Baziaka,[1] Apostolos Koronaios,[2] Anastasia Antonopoulou,[1] Vassiliki Markaki,[2] Pantelis Koutoukas,[1] Evangelos Papadomichelakis,[3] Thomas Tsaganos,[1] Apostolos Armaganidis,[3] Vassilios Koussoulas,[1] Anastasia Kotanidou,[2] Charis Roussos,[2] and Helen Giamarellou[1]

[1]Fourth Department of Internal Medicine, [2]First Department of Critical Care Medicine, and [3]Second Department of Critical Care Medicine, University of Athens Medical School, Athens, Greece; and [4]Department of Microbiology, University of Geneva Medical School, Geneva, Switzerland

Background. Because clarithromycin provided beneficiary nonantibiotic effects in experimental studies, its efficacy was tested in patients with sepsis and ventilator-associated pneumonia (VAP).

Methods. Two hundred patients with sepsis and VAP were enrolled in a double-blind, randomized, multicenter trial from June 2004 until November 2005. Clarithromycin (1 g) was administered intravenously once daily for 3 consecutive days in 100 patients; another 100 patients were treated with placebo. Main outcomes were resolution of VAP, duration of mechanical ventilation, and sepsis-related mortality within 28 days.

Results. The groups were well matched with regard to demographic characteristics, disease severity, pathogens, and adequacy of the administered antimicrobials. Analysis comprising 141 patients who survived revealed that the median time for resolution of VAP was 15.5 days and 10.0 days among placebo- and clarithromycin-treated patients, respectively ($P = .011$); median times for weaning from mechanical ventilation were 22.5 days and 16.0 days, respectively ($P = .049$). Analysis comprising all enrolled patients showed a more rapid decrease of the clinical pulmonary infection score and a delay for advent of multiple organ dysfunction in clarithromycin-treated patients, compared with those of placebo-treated patients ($P = .047$). Among the 45 patients who died of sepsis, time to death was significantly prolonged in clarithromycin-treated compared with placebo-treated patients ($P = .004$). Serious adverse events were observed in 0% and 3% of placebo- and clarithromycin-treated patients, respectively ($P = .25$).

Conclusions. Clarithromycin accelerated the resolution of VAP and weaning from mechanical ventilation in surviving patients and delayed death in those who died of sepsis. The mortality rate at day 28 was not altered. Results are encouraging and render new perspectives on the management of sepsis and VAP.

Severe sepsis and septic shock develop among >1,500,000 patients each year in North America and northern Europe, with a mortality rate range of 35%–50% [1]. This considerable case fatality rate has focused research attention on attempts to modulate the immune response of the host. Several clinical trials have examined the application of antiendotoxin and anti–TNF-α monoclonal antibodies and soluble receptors of TNF-α, but they failed to disclose considerable clinical benefit [2].

Clarithromycin, a macrolide, is beneficial in some pulmonary conditions, such as cystic fibrosis and diffuse panbronchiolitis [3]. Its mechanism of action is unclear, but, among other possible effects, anti-inflammatory properties have been suggested. In particular, clarithromycin inhibits the biosynthesis of proinflammatory cytokines by human mononuclear cells in vitro at concentrations of 2–10 μg/mL [4]. After intravenous administration, clarithromycin prolonged survival in an experimental model of acute pyelonephritis and sepsis caused by both susceptible and multiresistant gram-negative species. In these particular studies, clarithromycin administration was associated with a deceased secretion of proinflammatory mediators by blood monocytes without affecting bacterial growth [5–9].

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Reprints or correspondence: Dr. Evangelos J. Giamarellos-Bourboulis, Fourth Dept. of Internal Medicine, University General Hospital "ATTIKON," 1 Rimini St., 124 64 Athens, Greece (giamarel@ath.forthnet.gr).

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The present clinical trial was designed to test the efficacy of clarithromycin in sepsis associated with ventilator-associated pneumonia (VAP), a frequent and severe complication of mechanical ventilation in the intensive care unit (ICU) [10]. Selecting a single cause of sepsis for this study eliminates the possible bias introduced in some earlier studies, in which heterogeneous infections were combined for analysis [2].

PATIENTS AND METHODS

Study design. The study was a prospective, double-blind, randomized, placebo-controlled, multicenter clinical trial that was approved by the ethics committees of all hospitals of the participating study sites and by the National Organization for Medicines of Greece (http://www.clinicaltrials.gov/; registration number NCT00297674). During the period from June 2004 until November 2005, 218 patients were screened and 200 patients were enrolled (figure 1). After assigning 80% power to achieve a >5% 2-sided difference between the 2 arms of treatment regarding mortality and resolution of VAP, 100 patients were assigned to receive placebo and 100 were assigned to receive clarithromycin. The mortality of the entire study population was assessed during follow-up, and because no deviation was observed from the expected rate, no interim analysis was planned; the study was concluded when the last patient of 200 was enrolled. Patients were hospitalized at the Fourth Department of Internal Medicine of "ATTIKON" University General Hospital, the First Department of Critical Care of "Evangelismos" General Hospital, and the Second Department of Critical Care of "ATTIKON" University General Hospital (all in Athens, Greece). The research microbiology laboratory of the Fourth Department of Internal Medicine acted as the central laboratory for the study.

Inclusion criteria were as follows: (1) written informed consent provided by first- or second-degree relatives, (2) patient intubation and mechanical ventilation for at least 48 h before enrollment, (3) age ⩾18 years, (4) diagnosis of VAP, and (4) signs of sepsis. As a rule, written informed consent was asked of the patients' relatives on the third day after hospital admission.

Exclusion criteria were as follows: (1) neutropenia, defined as a neutrophil count <500 cells/μL; (2) HIV infection; (3) oral intake of corticosteroids at a dose ⩾1 mg/kg of equivalent prednisone for a period >1 month; (4) administration of drotrecogin alfa in the previous 5 days; and (5) atrioventricular block of second or third degree.

VAP was diagnosed in patients who presented with all of the following: (1) new or persistent consolidation on lung radiography, (2) purulent tracheobronchial secretions (TBSs), and (3) a clinical pulmonary infection score (CPIS) >6 [11–15]. The CPIS was determined as assessed by Pugin et al. [16].

Sepsis was defined as the presence of at least 2 of the following [17]: (1) a core temperature >38°C or <36°C, (2) partial pressure of carbon dioxide <32 mm Hg, (3) pulse rate >90/min, and (4) WBC count >12,000 cells/μL or <4,000 cells/μL

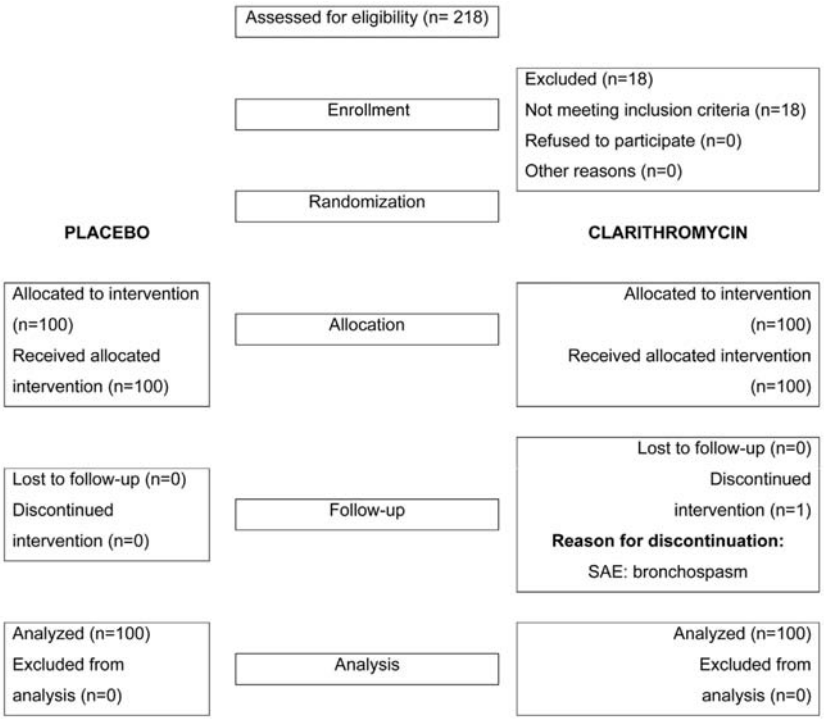

Figure 1. Stages of the double-blind, randomized, placebo-controlled trial, with the number of patients at each stage. SAE, serious adverse event.

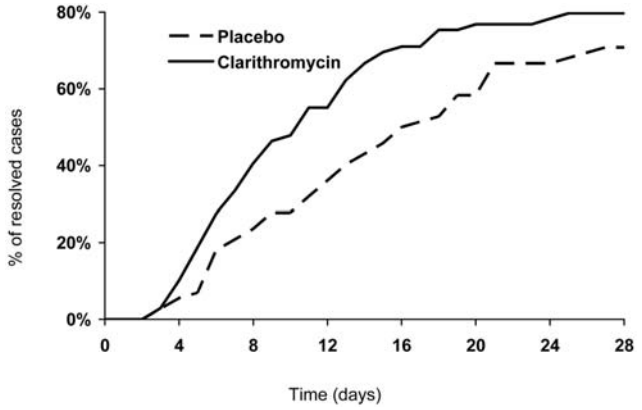

Figure 2. Cumulative incidence of the resolution of ventilator-associated pneumonia within the follow-up period of 28 days. Analysis comprised patients who survived until the 28th day ($n = 141$). $P = .036$, by Mantel-Cox log rank test; $P = .017$, by Tarone-Ware test; $P = .011$, by the Breslow test.

or >10% of band forms. Severe sepsis was defined as sepsis accompanied by at least 1 organ failure, as described elsewhere [17]. Septic shock was defined as sepsis accompanied by a systolic blood pressure <90 mm Hg, necessitating the administration of vasopressors for >1 h [17].

Administration of treatment. Patients were randomly assigned to receive either placebo or clarithromycin treatment. The allocated sequence was generated by an independent biostatistician. The study drug was prepared by an unblind investigator who had access to the randomization table; he did not participate in any other stage of the study. Sealed envelopes were used to implement the random allocation sequence. The study drug was administered once daily within 1 h for 3 consecutive days by a nurse blind to treatment group. Each dose of clarithromycin was 1 g. More precisely, 500 mg of white amorphous powder contained in each of 2 vials (Abbott) was dissolved in 20 mL of water for injection and was diluted to a final volume of 250 mL of 5% glucose in water. Placebo consisted of 20 mL of water for injection diluted to 250 mL of 5% glucose in water. Administration was performed by an infusion pump at a rate of 4.16 mL/min through a catheter connected to a subclavian vein. The dosing of clarithromycin, 1 g/day, was that recommended by the manufacturer. The total daily dose was administered in a single infusion, not in 2 infusions as usual, to provide higher serum concentrations. This approach was likely to provide at least 2 μg/mL in the serum [18], a concentration shown to inhibit biosynthesis of IL-8 by human monocytes [4] even in patients with septic shock and increased volumes of distribution. All enrolled patients received concomitant antimicrobials for the treatment of VAP as prescribed by their attending physicians.

Evaluation of patients. Patients were observed for 28 days. The following variables were recorded at baseline and follow-up: (1) vital signs; (2) Acute Physiology and Chronic Health Evaluation (APACHE) II score; (3) laboratory examination results; (4) blood gases and the ratio of partial pressure of oxygen (PO_2) to fraction of inspired oxygen (FiO_2); (5) lung radiological findings; (6) morphological appearance of TBSs; (7) administered antimicrobial agents, vasopressors, hydrocortisone, and insulin; and (8) positive blood culture results. For each day of placebo or clarithromycin administration, all coadministered medications were recorded, and a 12-lead electrocardiogram was performed with estimation of QTc. Daily visits were performed at the same time of day as administration of the first dose of the study drug.

Quantitative TBS cultures were performed at baseline and on the fifth and tenth days of follow-up. Samples of TBSs were collected after insertion of a sterile catheter into the intubation tube or into the tracheotomy connected to a negative-pressure device and were transported within 1 h to the central laboratory. A total of 0.5 mL of TBS was added into a sterile tube with 0.5 mL of 1 mg/mL of dithiothreitol (Oxoid) and was diluted 5 consecutive times (1:10). Aliquots of 0.1 mL of each dilution were plated onto MacConkey and blood agar (Becton Dickinson). Dishes were incubated for 5 days at 35°C. Cultures that yielded a pathogen at a count of $\geqslant 1 \times 10^6$ colony-forming units/mL were considered to be positive [19]. Identification of pathogens was performed by the API20E and the API20NE systems (bioMérieux). Susceptibility of the isolated pathogens to antimicrobials was performed by the Kirby-Bauer disk diffusion method with interpretation criteria according to the Clinical and Laboratory Standards Institute [20].

A serious adverse event (SAE) was considered to be any unexpected event that (1) led to death, (2) put the patient's life in danger, (3) prolonged hospitalization, (4) was accompanied by permanent or considerable disability, or (5) was ac-

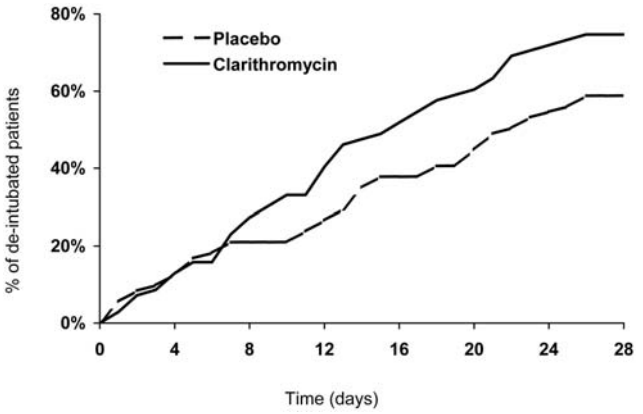

Figure 3. Cumulative time to weaning from mechanical ventilation among placebo-treated and clarithromycin-treated patients. Analysis comprised patients who survived until the 28th day ($n = 141$). $P = .049$, by Mantel-Cox log rank test.

Table 1. Baseline characteristics of study patients with sepsis due to ventilator-associated pneumonia (VAP).

Variable	Treatment with		*P*
	Placebo (n = 100)	Clarithromycin (n = 100)	
Age, mean years ± SD	58.40 ± 17.41	58.41 ± 20.74	.89
Age ⩾65 years, no. (%)	50 (50)	55 (55)	.48
Sex, M/F	73/27	74/26	1
APACHE II score, mean score ± SD	17.32 ± 6.23	16.88 ± 5.99	.37
CPIS, mean score ± SD			
At baseline	7.92 ± 1.94	7.62 ± 0.93	.29
On day 5	6.10 ± 2.43	5.23 ± 2.51	.016
On day 10	5.88 ± 2.32	5.09 ± 2.48	.032
WBC count, mean cells/μL ± SD	13,144.4 ± 6701.1	11,390.4 ± 4591.7	.20
PO_2:FiO_2, mean ± SD	218.5 ± 110.3	224.8 ± 103.2	.45
Reason for intubation, no. (%)			.82
Respiratory failure due to chronic obstructive pulmonary disease	44 (44)	43 (43)	
Multiple injuries	19 (19)	19 (19)	
Cerebral ischemic attack or hemorrhage	21 (21)	26 (26)	
Intra-abdominal infection	4 (4)	7 (7)	
Celiac aortic aneurysm replacement	7 (7)	6 (6)	
Other(s)	13 (13)	10 (10)	
Predisposing factors, no. (%)			.55
Diabetes mellitus type 2	14 (14)	16 (16)	
Coronary heart disease	12 (12)	15 (15)	
Hypertension	10 (10)	8 (8)	
Cardiac failure	9 (9)	6 (6)	
Other(s)	10 (11)	11 (11)	
No. of patients with early/late VAP	44/56	41/59	.78
Time between ICU admission and VAP diagnosis, median days (IQR)	9.00 (3–48)	8.50 (3–54)	.99
Administration of hydrocortisone, proportion (%) of patients	25/100 (25)	22/100 (22)	.74
Administration of insulin, proportion (%) of patients	39/100 (39)	35/100 (35)	.53
Critical illness, no. (%) of patients			.95
Sepsis	26 (26)	25 (25)	
Severe sepsis	31 (31)	33 (33)	
Septic shock	43 (43)	42 (42)	
⩾10^6 CFU/mL in TBS, no. (%)	68 (68)	66 (66)	.88
Type of pathogen, no. (%) of patients			.28
Pseudomonas aeruginosa	12 (17.6)	17 (25.8)	
Acinetobacter baumannii	43 (63.2)	36 (54.5)	
Klebsiella pneumoniae	6 (8.8)	5 (7.6)	
Enterobacter species	2 (2.9)	4 (6.1)	
Stenotrophomonas maltophilia	2 (2.9)	0 (0)	
Providentia stuartii	0 (0)	1 (1.5)	
Other(s)	3 (4.4)	3 (4.5)	
Incidence of bacteremia by the same isolate, no. (%) of patients	21 (21)	26 (26)	.37
Type of administered antimicrobial agent, no. (%) of patients			.11
Piperacillin-tazobactam	9 (9)	12 (12)	
Carbapenem and vancomycin-linezolid	38 (38)	34 (34)	
Carbapenem, colistin, and vancomycin-linezolid	27 (27)	31 (31)	
Carbapenem monotherapy	8 (8)	4 (4)	
Third-generation cephalosporins and clindamycin	16 (16)	16 (16)	
Fluoroquinolones	2 (2)	1 (3)	
Colistin	0 (0)	1 (1)	

(continued)

Table 1. ***(Continued.)***

Variable	Treatment with		*P*
	Placebo ($n = 100$)	Clarithromycin ($n = 100$)	
Susceptibility of the TBS isolate to the administered antimicrobials, proportion (%) of patients with isolate	42/67 (62.7)	49/65 (75.4)	.44
Time between diagnosis of VAP and start of appropriate antimicrobial therapy, median days (IQR)	0 (0–12)	0 (0–8)	.93
Eradication of the pathogen on day 5, proportion (%) of patients with isolate	17/67 (25.4)	22/65 (33.8)	.31
Eradication of the pathogen on day 10, proportion (%) of patients with isolate	21/67 (31.3)	19/65 (29.2)	.82

NOTE. APACHE, Acute Physiology and Chronic Health Evaluation; CFU, colony-forming unit; CPIS, clinical pulmonary infection score; ICU, intensive care unit; IQR, interquartile range; PO_2:FiO_2, ratio of partial pressure of oxygen to fraction of inspired oxygen; TBS, tracheobronchial secretion.

companied by any grade IV laboratory abnormality. Organ failure and death related to sepsis were not assessed as SAEs.

Resolution of VAP encompassed all of the following, which were assessed daily by the attending physicians: (1) absence of purulent material in TBSs, (2) improvement of the infiltrate on the lung radiography, (3) increase of the ratio of partial pressure of oxygen to fraction of inspired oxygen, and (4) resolution of the signs of sepsis that led to study enrollment. Times to resolution of VAP and deintubation were recorded. Case reports were confirmed by a monitor blind to treatment group.

Statistical analysis. Unblinding for the study drug was performed when follow-up of all patients was completed. Primary end points were the number of days until resolution of VAP, number of days receiving mechanical ventilation, and mortality due to sepsis. The last was indirectly defined after exclusion of all cases in which no clear relationship between death and the underlying septic process could be found. All end points were right censored on the 28th day.

Quantitative parameters were expressed by their mean ± SD when they followed a normal distribution or by their median and interquartile range (IQR) for nonparametric parameters, as assessed by Kolmogorov-Smirnov statistics and compared by Student's *t* test or by Mann-Whitney *U* test, respectively. Comparisons of qualitative characteristics were performed by the χ^2 test.

The cumulative incidence of the resolution of VAP and of weaning from the ventilator during the study period was determined in patients who survived until the 28th day. The cumulative time to death from sepsis was also determined for patients who died. Comparisons were performed by the Mantel-Cox log-rank test, the Tarone-Ware test, and the Breslow test. The impact of various factors on the cumulative incidence of the resolution of VAP within the period of 28 days was assessed by stepwise Cox regression analysis. These factors comprised type of therapy, sex, age >65 years, presence of septic shock, and APACHE II score >15. Hazard ratios and 95% CIs were estimated.

The most significant factor that affected survival was determined by Mantel-Haenszel statistical analysis. The effect of that factor was separately evaluated for each group and was compared with the Breslow-Day and Tarone tests. Any 2-sided *P* value <.05 was considered to be statistically significant.

RESULTS

Study population. The first patient was enrolled on 23 June 2004, and the last was enrolled on 24 November 2005. Both groups of patients were well matched for demographic characteristics, underlying conditions, severity of sepsis, VAP-causing microorganisms, adequacy of and time to antibiotic treatment, and eradication rates of causative bacteria (table 1). No patient received a macrolide other than the study drug.

Effect of clarithromycin on resolution of VAP. On the 28th day, 141 patients were alive. In the placebo group (72 survivors), VAP resolved in 52 (72.2%) of cases within a median time of 15.5 days (25% and 75% interquartiles, 8.0 and >28.0 days, respectively). In the clarithromycin group (69 survivors), VAP resolved in 55 (79.7%) of the cases within a median time of 10.0 days (25% and 75% interquartiles, 5.0 and 18.0 days, respectively). Curves of the cumulative percentages of the resolution of VAP during the follow-up reveal a significant difference between the 2 groups (figure 2). Cox regression analysis of the cumulative incidence of the resolution of VAP revealed that the only parameter that shifted the baseline function in a significant manner was the administration of clarithromycin (hazard ratio, 1.48; 95% CI, 1.00–2.20; $P = .048$).

When statistical analysis considered all enrolled patients, VAP resolved in 54 of placebo-treated and in 61 of clarithromycin-treated patients, with an earlier resolution in the latter group (table 2). Among them, 38 and 39 patients, respectively, received an adequate initial antimicrobial agent. Median (IQR) times of resolution were 12 (2 to >28) days and 8 (2–24) days, respectively ($P = .017$, by comparison of the groups). In patients whose VAP resolved, new infection and sepsis emerged in 11 (20.4%) and 16 (26.3%) in the 2 groups, respectively ($P = .37$).

Table 2. Primary study outcomes as assessed in the registry of the trial.

Outcomes	Treatment with		*P*
	Placebo (n = 100)	Clarithromycin (n = 100)	
Crude mortality for any reason	28	31	.76
Mortality at 7 days	8	6	.78
Sepsis-related mortality at 28 days, no. of patients/total patients, excluding those who died of other causes (%)	24/96 (25.0)	21/90 (23.3)	.86
Progression to MODS among the total enrolled patients	8	14	.26
Time until progression to MODS, mean days ± SD	3.38 ± 1.06	5.78 ± 3.52	.047
Time until resolution of VAP, median days (IQR)	11.5 (2 to >28)	7.0 (2–24)	.006
Time in ICU after diagnosis of VAP for patients who survived, mean days ± SD	21.58 ± 8.22	23.36 ± 7.05	.17

NOTE. Data are no. of patients, unless otherwise indicated. Clinical registry of the trial (NCT00297674) is available at http://www.clinicaltrials.gov/. ICU, intensive care unit; IQR, interquartile range; MODS, multiple-organ dysfunction; VAP, ventilator-associated pneumonia.

Effect of clarithromycin on duration of mechanical ventilation. Analysis comprised the 141 patients who survived until day 28. Weaning from mechanical ventilation occurred in 42 (58.6%) of placebo-treated patients within a median period of 22.5 days (25% and 75% interquartiles, 12.0 and >28.0 days, respectively). Weaning from mechanical ventilation occurred in 50 (72.5%) of clarithromycin-treated patients within a median period of 16.0 days (25% and 75% interquartiles, 8.0 and >28.0 days, respectively). Curves of the cumulative percentages of weaning from mechanical ventilation over time showed that clarithromycin was beneficial (figure 3).

Effect of clarithromycin on mortality. Fourteen patients died of a cause other than sepsis and were therefore excluded from this analysis. Among the 186 remaining patients, 49 died of sepsis: 24 (25.0%) of 96 patients in the placebo group and 21 (23.3%) of 90 patients in the clarithromycin group (P = .463, by comparison of the groups). Time to death was significantly prolonged among patients treated with clarithromycin (figure 4).

The most significant factor associated with sepsis-related death was the copresence of septic shock and multiple-organ dysfunction (MODS), with a common OR of 7.70 (95% CI, 3.65–16.23; P < .001). The OR was 19.00 (95% CI, 5.64–64.03) among placebo-treated patients and was 3.78 (95% CI, 1.36–10.45) among clarithromycin-treated patients (P = .043).

Adverse events. No study-drug–related SAE (0%) was observed among patients receiving the placebo; 3 study-drug–related SAEs (3%) were reported among patients treated with clarithromycin (P = .25). These SAEs included 1 episode of bronchospasm 1 h after the end of administration of the study drug on the second day. It occurred on an attempt at weaning and was fully resolved; the patient discontinued treatment. Two episodes of an increase in liver aminotransferase levels of 10 times the upper normal limit occurred. In the first patient, elevation started 2 days before enrollment and became 10 times the upper normal limit after the third dose of clarithromycin. The elevation began to resolve within 3 days, in parallel with discontinuation of coadministered meropenem. In the second patient, elevation started on the second day after enrollment and began to resolve after 2 days. Both patients remained part of the study.

DISCUSSION

Intravenous administration of clarithromycin for 3 days was associated with earlier resolution of VAP, more rapid decrease of CPIS on days 5 and 10, earlier weaning from mechanical ventilation in surviving patients, later death in those who died of sepsis, and prolongation of the time of progression to MODS. Although the ORs for death due to septic shock and MODS were significantly decreased, globally, overall mortality among study patients was not affected. Only 3 SAEs occurred.

These results may imply a dual action of clarithromycin in

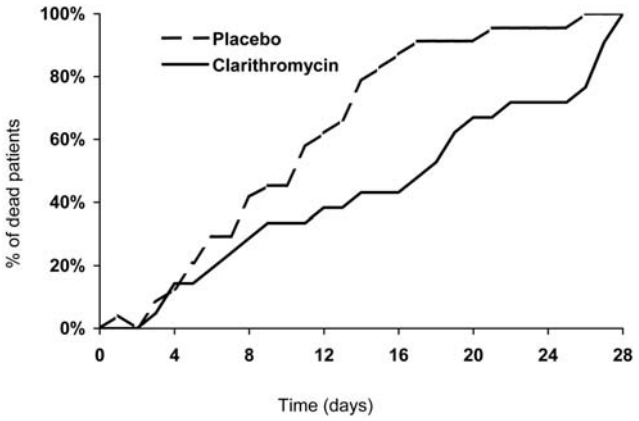

Figure 4. Cumulative time to death from sepsis among placebo-treated and clarithromycin-treated patients. Analysis comprised 24 placebo-treated patients and 21 clarithromycin-treated patients who died, within the follow-up period of 28 days, of sepsis due to ventilator-associated pneumonia. P = .004, by Mantel-Cox log rank test; P = .030, by Tarone-Ware test; P = .011, by the Breslow test.

the study population. This action comprises (1) a shortening of the physical course of VAP by 1.48 times, corresponding to a median duration of 5.5 days (figure 2), which was accompanied by a median reduction of 6.5 days of the time mechanical ventilation was needed (figure 3), and (2) an effect on the septic process itself, because the times to death from sepsis and to progression to MODS were prolonged even if the overall mortality due to sepsis was not affected (figure 4 and table 2). The reduction of mechanical ventilation duration achieved with clarithromycin treatment suggests an effect of the macrolide drug on the respiratory function. In practical terms, we assume that earlier weaning from the mechanical ventilation exposed the patient to less risk of ventilator-associated infectious complications. Earlier resolution of VAP by clarithromycin did not increase the risk of new infections, in contrast with recent results that showed a positive correlation between methicillin-resistant *Staphylococcus aureus* infection and former use of azithromycin [21].

Although more-invasive techniques may provide better microbiological definitions, identification of the underlying pathogen was achieved in almost 70% of patients (134 patients). The pathogens were gram-negative organisms in all cases, and their eradication rate was similar in both groups (table 1). This finding is in contrast to epidemiologic results from other countries, such as the United States, where gram-positive bacteria predominate in VAP [22]. In Greece, multidrug-resistant gram-negative species of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are implicated in both early and late VAP; when *S. aureus* emerges, it is resistant to methicillin and macrolides [23, 24]. The microbial causes of VAP in other European countries also identified multidrug-resistant gram-negative species as the main pathogens [10, 25].

The mechanism of action of clarithromycin in our patients is difficult to assess, and only hypotheses can be raised. A conventional antibiotic effect is unlikely, with consideration of the gram-negative microbiology found in our patients. However, a series of publications suggest a beneficial effect of macrolides on the host in patients with chronic inflammatory disorders of the airways and in animal models of infection. Diffuse panbronchiolitis, cystic fibrosis, and bronchiectasis are chronic disorders characterized by exacerbations of infections; patients are often colonized with *P. aeruginosa.* Macrolides improve function of the lung by reducing infective exacerbations and inhibit recruitment of neutrophils by reducing production of IL-8. Moreover, they reduce sputum production and expectoration [3, 26–28]. In vitro studies attributed their sputum production and expectoration effect on their action on the tight junctions between epithelial cells of the airways [29]. In the patients colonized with *P. aeruginosa,* macrolides may also act as inhibitors of quorum sensing among bacteria that colonize the airways [30]. Twenty-one infants with acute bronchiolitis caused by the respiratory syncytial virus participated in a double-blind, placebo-controlled trial [31]; 12 received oral clarithromycin, 500 mg twice daily, for 3 weeks. Results showed a clear decrease of the need for oxygen supplementation and of the length of hospitalization in the clarithromycin arm compared with results of the placebo-treated infants. An immunomodulatory effect of clarithromycin seemed probable, since serum concentrations of IL-4 and IL-8 were significantly decreased and the drug does not possess any antiviral activity.

Animal studies with acute pyelonephritis and sepsis by gram-negative pathogens of *Escherichia coli, Klebsiella pneumoniae,* and *P. aeruginosa* have shown that intravenous administration of clarithromycin prolonged survival and reduced concentrations of TNF-α in serum. The inflammatory reactions of tissues were attenuated by clarithromycin without any change of tissue bacterial load, whereas blood monocytes released lower amounts of TNF-α [5–9]. These results favor the hypothesis for an immunomodulatory effect of clarithromycin on the inflammatory cells of the host.

The presented results deserve consideration for at least 3 reasons. First, significant differences appeared despite the small size of the population sample (100 patients per arm). Second, enrolled patients were severely ill, with mean APACHE II scores >17 and mean CPISs >7. Accordingly, 59 patients (29.5%) died during the 28-day period of observation, including 45 (22.5%) deaths due to sepsis. Third, clarithromycin was administered for only 3 days, a short period for the results obtained.

In conclusion, we consider our results to be encouraging. However, to fully establish the actual potential of clarithromycin in sepsis, other studies will have to be performed, with larger populations and a prolonged clarithromycin regimen. The relative good toleration seems to allow it.

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