ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2007, p. 3977–3982 Vol. 51, No. 11
0066-4804/07/$08.00+0 doi:10.1128/AAC.00006-07

Comparison of β-Lactam and Macrolide Combination Therapy versus Fluoroquinolone Monotherapy in Hospitalized Veterans Affairs Patients with Community-Acquired Pneumonia▽

Thomas P. Lodise,[1,2]* Andrea Kwa,[1,3] Leon Cosler,[1] Reetu Gupta,[1] and Raymond P. Smith[4]

Albany College of Pharmacy,[1] Ordway Research Institute,[2] and Stratton VA Medical Center,[4] Albany, New York, and Singapore General Hospital, Singapore[3]

Received 3 January 2007/Returned for modification 18 February 2007/Accepted 10 August 2007

Data comparing the treatment outcomes of the two most frequently recommended empirical antibiotic regimens for community-acquired pneumonia (CAP)—combination therapy with an extended-spectrum β-lactam and a macrolide (BL+M) or fluoroquinolone (F) monotherapy—for patients with severe CAP are sparse. The purpose of this study was to compare empirical BL+M combination therapy with F monotherapy for Veterans Affairs (VA) patients with severe CAP. This retrospective study included patients with CAP who received empirical therapy with BL+M or F between October 1999 and May 2003 in the Upstate New York VA Network. Outcome measures were 14-day mortality, 30-day mortality, and length of hospital stay (LOS). Severe CAP was defined as a class V pneumonia severity index (PSI). During the study period, 261 patients received BL+M and 254 received F. Disease severity was similar for the two treatment groups at admission, and the presence of tachycardia was the only difference noted. For PSI class V patients, there were lower 14-day and 30-day mortality rates with BL+M than with F (14-day rates, 8.2% versus 26.8% [$P = 0.02$]; 30-day rates, 18.4% versus 36.6% [$P = 0.05$]). No differences in mortality between treatment groups were noted for the lower PSI classes. The overall median LOS was significantly longer for the BL+M combination group than for the F monotherapy group (6.0 days versus 5.0 days, respectively [$P = 0.01$]), but no difference in LOS was noted among PSI class V patients. Our study showed that improved outcomes may be realized with BL+M in cases of severe CAP. A randomized clinical study is warranted based on these results.

Community-acquired pneumonia (CAP) is a common infection associated with considerable morbidity, mortality, and costs (3, 17, 18, 27, 40, 44). Management of CAP has been further complicated by the emergence of antibiotic resistance, particularly among *Streptococcus pneumoniae* strains (5). Published guidelines for the management of CAP provide health care practitioners with current, evidence-based standards for antimicrobial therapy, yet even this expert guidance is sometimes conflicting (2, 20, 29, 34). The two most frequently recommended antibiotic regimens for hospitalized patients with CAP are (i) an extended-spectrum β-lactam (an extended-spectrum cephalosporin or a β-lactam–β-lactamase inhibitor) with a macrolide or (ii) an antipneumococcal quinolone. These regimens have activity against the major causes of CAP, including drug-resistant *Streptococcus pneumoniae* (2, 20, 29, 34).

Despite similar spectra of activity and favorable resistance patterns against CAP pathogens, emerging evidence suggests the superiority of dual therapy over monotherapy for certain populations, particularly patients with severe CAP or bacteremic pneumococcal CAP (1, 4, 11, 16, 21, 31, 33, 42, 43). It is not clear if any specific combination of agents is most effective, but most studies have examined the efficacy of combining an extended-spectrum cephalosporin and a macrolide (4, 11, 16, 31, 33, 42). Conversely, several studies have refuted the advantages of combination therapy over monotherapy for severe CAP (5, 13, 19). Data comparing the outcomes of the two most frequently recommended empirical antibiotic regimens for CAP (dual therapy with an extended-spectrum β-lactam and a macrolide or montherapy with an antipneumococcal quinolone) for patients with severe CAP are sparse.

While the impact of empirical CAP antibiotic selection on outcomes has been evaluated in various patient care settings, limited information exists for Veterans Affairs (VA) patients (14, 28), and we are unaware of any published CAP study that specifically examines the impact of combination therapy versus monotherapy for VA patients with severe CAP. It is difficult to generalize the findings of other studies to VA patients because of the vast differences in study populations: VA patients are typically older, with multiple comorbidities. This study informs the dual-therapy-versus-monotherapy debate by comparing an extended-spectrum β-lactam antibiotic-and-macrolide combination to monotherapy with a fluoroquinolone for hospitalized VA patients with severe CAP.

(The results of this study were presented in part as a poster presentation at the 42nd Annual Meeting of the Infectious Diseases Society of America, Boston, MA, October 2004.)

MATERIALS AND METHODS

Setting. The study was performed at the Upstate New York VA Health Network, or Veterans Integrated Service Network 2 (VISN 2), which is an integrated health care system that provides medical care and services to the U.S. military veterans of upstate New York and surrounding areas. It comprises five hospitals in upstate New York (Albany, Bath, Buffalo, Canandaigua, and Syracuse) and numerous satellite health care centers throughout the region.

* Corresponding author. Mailing address: Pharmacy Practice, Albany College of Pharmacy, 106 New Scotland Avenue, Albany, NY 12208-3492. Phone: (518) 445-7292. Fax: (518) 445-7302. E-mail: lodiset@acp.edu.

▽ Published ahead of print on 20 August 2007.

Study design and population. A retrospective cohort study included all patients hospitalized with a diagnosis of CAP in the VISN 2 database between 1 October 1999 and 31 May 2003. This study was approved (expedited) by the Stratton VA institutional review board.

Inclusion criteria. Only patients who satisfied the Infectious Diseases Society of America (IDSA) definition of CAP (2, 29) were included: those who (i) were immunocompetent (absolute neutrophil count, ≥1,000 cells/mm^3), (ii) had an acute illness (symptom onset within 10 days), (iii) had a new chest radiographic infiltrate confirmed by a radiologist, and (iv) had clinical signs suggestive of acute pneumonia, including either one major criterion (fever [temperature over 37°C], hypothermia [temperature less than 36°C], cough, or sputum production) or two minor criteria (dyspnea, pleuritic pain, clinical evidence of lung consolidation, or a leukocyte count higher than 10,000 cells/mm^3 or lower than 4,500 cells/mm^3). For this study, patients must also have received either an extended spectrum β-lactam and a macrolide or levofloxacin (the only fluoroquinolone approved for use in VISN 2 during the study period) within the first 24 h after presentation to the hospital and must have remained on therapy for at least 48 h after admission.

Exclusion criteria. Patients were excluded if (i) they died within the first 24 h after presentation to the hospital, (ii) they received any other antibiotics during the first 48 h of hospital presentation, or (iii) they were hospitalized or resided in a long-term care facility for at least 14 days in the 30 days prior to admission.

Patient data. A structured data instrument collected the following data from the patients' electronic medical records: demographic factors, medical history and comorbid diseases, physical examination and laboratory findings, prior antibiotic therapy, previous episodes of pneumonia in the past 180 days, severity of illness at collection (calculated by means of the Pneumonia Severity Index [PSI] scoring system [15] and the Acute Physiological and Chronic Health Evaluation [APACHE-II] score [25]), microbiological culture results, and antibiotic treatment. The presence of the following comorbid conditions was documented: diabetes mellitus, human immunodeficiency virus infection, neoplastic disease, liver disease, heart failure, and cerebrovascular and renal disease. The PSI and APACHE-II scores were calculated based on the worst physiological score derived from physical and laboratory findings collected at admission. Prior antibiotic use was defined as the administration of antimicrobials for at least 48 h in the 180 days before admission.

Microbiology. Microbiological data included all positive respiratory and blood cultures collected within the first 24 h of admission. Positive pneumococcal and *Legionella* urinary antigen assay results were also documented. Etiologic CAP diagnosis was based on IDSA recommendations (2, 29). A definite etiology was established by the recovery of a probable etiologic agent from an uncontaminated specimen (blood, pleural fluid, transtracheal aspirate, or transthoracic aspirate) or the recovery from respiratory secretions of a likely pathogen that does not colonize the upper airways. A probable etiologic diagnosis was established by detection (by staining or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, bronchoscopic aspirate, or quantitatively cultured bronchoscopic bronchoalveolar lavage fluid or brush catheter specimen). With semiquantitative culture, the pathogen had to be recovered in moderate to heavy growth in the presence of moderate to heavy polymorphonuclear cells and minimal to no squamous epithelial cells.

Outcomes. The following clinical outcomes were collected: (i) vital status 14 days after hospital admission (14-day mortality), (ii) vital status 30 days after hospital admission (30-day mortality), and (iii) length of hospital stay (LOS). Outcomes were compared between treatment groups for the entire population and were also compared among the five PSI classes. Severe pneumonia was defined as a PSI score of V.

Data analysis. Qualitative variables were compared by the Pearson χ^2 test or Fisher's exact test, and quantitative variables were compared by Student's *t* test or the Mann-Whitney U test. Multivariate analyses were performed to determine the independent association of treatment with the outcome of interest while adjusting for confounding variables (variables found to be significantly different between treatment groups). For all analyses, a P value of <0.05 was considered significant for two-tailed tests. SYSTAT for Windows (version 11.0) was used for all calculations.

RESULTS

A total of 1,560 VISN 2 patients were hospitalized with a diagnosis of CAP during the study period; 845 of these patients satisfied the IDSA CAP definition, did not die within the first 24 h after presentation to the hospital, and had not been hospitalized or resided in a long-term care facility for ≥14 days in the 30 days prior to admission. Of the 845 CAP patients, 515 received either combination therapy consisting of a β-lactam and a macrolide (261 patients) or fluoroquinolone monotherapy (254 patients) for at least 48 h after admission. The empirical antibiotic regimens provided to the other CAP patients during the first 48 h after admission are shown in Table 1. All patients in the fluoroquinolone monotherapy group received levofloxacin. Of the 261 patients in the β-lactam-plus-macrolide combination therapy group, 237 (91%) received an extended-spectrum cephalosporin with azithromycin and 24 (9%) received a β-lactam–β-lactamase inhibitor combination antibiotic with azithromycin.

TABLE 1. Empirical antibiotic regimens provided to patients who met IDSA CAP criteria[a]

Empirical treatment regimen	No. (%) of patients
β-Lactam–macrolide	261 (30.9)
Fluoroquinolone alone	254 (30.1)
β-Lactam alone	168 (19.9)
β-Lactam–fluoroquinolones	43 (5.1)
Macrolide alone	33 (3.9)
Other	86 (10.2)

[a] See references 2 and 29.

Bivariate comparisons of baseline clinical and laboratory characteristics between treatment groups are shown in Table 2. The two groups were similar with respect to age, gender, comorbid diseases, most aspects of physical examination and laboratory findings, prior episodes of CAP, prior antibiotic use, and mean PSI and APACHE-II scores. The proportion of patients who had tachycardia (pulse rate, ≥125/min) was significantly higher in the combination therapy arm than in the fluoroquinolone monotherapy arm. Although the proportions of patients with tachycardia were different in the two groups, no significant differences in outcomes (14-day mortality, 30-day mortality, and LOS) were noted between patients with and without tachycardia ($P > 0.4$ for all comparisons). Bivariate comparisons of baseline clinical and laboratory characteristics between treatment groups for patients with severe pneumonia (PSI category V) are also shown in Table 2. Within PSI category V, the treatment groups were similar with respect to clinical and laboratory characteristics. The groups differed significantly only in the proportion of patients with tachycardia, which was higher among PSI category V patients who received combination therapy. Again, although the proportions of patients with tachycardia were different for the two treatment groups, no significant differences in outcomes (14-day mortality, 30-day mortality, and LOS) were noted between PSI category V patients with and without tachycardia ($P > 0.6$ for both comparisons). Lastly, the causative CAP pathogens and the proportions of patients with bacteremic CAP were similar for the two treatment groups (Table 3). Eight patients who received β-lactam-plus-macrolide combination therapy and four patients who received fluoroquinolone montherapy had pneumococcal bacteremia.

Overall, there were no differences in 14-day and 30-day mortality rates between groups (Table 4). Among patients with severe pneumonia (PSI category V), the 14-day mortality rate was significantly lower for those receiving combination therapy

TABLE 2. Comparison of clinical characteristics between patients receiving empirical combination therapy (β-lactam and macrolide) versus empirical monotherapy (fluoroquinolone)[a]

Characteristic	Overall			PSI V		
	BL+M (n = 261)	F (n = 254)	P	BL+M (n = 49)	F (n = 41)	P
Age (yr [mean ± SD])	70.6 ± 12.6	71.6 ± 11.4	0.4	79.7 ± 7.3	78.3 ± 6.3	0.3
Male gender	257 (98.5)	247 (97.2)	0.4	48 (98.0)	40 (97.6)	0.9
Race			0.4			0.9
White	206 (79.2)	200 (79.1)		42 (85.7)	32 (78.0)	
African-American	17 (6.5)	25 (9.9)		0 (0)	5 (12.2)	
Hispanic	2 (0.8)	2 (0.8)		0 (0)	0 (0)	
Other	2 (0.8)	0 (0)				
Not reported	33 (12.7)	26 (10.3)		7 (14.3)	4 (9.8)	
Clinical findings						
Diabetes mellitus	82 (31.4)	88 (34.6)	0.4	21 (42.9)	16 (39.0)	0.7
Prior episodes of CAP	48 (18.4)	45 (17.7)	0.8	9 (18.4)	7 (17.1)	0.9
Prior antibiotic therapy	106 (40.6)	121 (47.6)	0.1	22 (44.9)	18 (43.9)	0.9
HIV	10 (3.8)	3 (1.2)	0.1	0 (0)	0 (0)	NA
Liver disease	17 (6.5)	14 (5.5)	0.7	4 (8.2)	4 (9.8)	0.8
Cerebrovascular disease	41 (15.7)	39 (15.4)	0.9	15 (30.6)	12 (29.3)	0.9
Neoplastic disease	79 (30.3)	81 (31.9)	0.7	27 (55.1)	24 (58.5)	0.7
CHF	73 (28.0)	61 (24.0)	0.4	27 (55.1)	17 (41.5)	0.2
Renal disease	44 (16.9)	32 (12.6)	0.2	18 (36.7)	10 (24.4)	0.2
Physical examination findings						
Altered mental status	4 (1.5)	4 (1.6)	1.0	3 (6.1)	1 (2.4)	0.6
Respiratory rate, ≥30/min	17 (6.5)	17 (6.7)	0.9	7 (14.3)	10 (24.4)	0.2
Systolic blood pressure, <90 mm Hg	8 (3.1)	6 (2.4)	0.6	4 (8.2)	2 (4.9)	0.7
Temp, <35°C or >40°C	7 (2.7)	5 (2.0)	0.6	3 (6.1)	4 (9.8)	0.7
Pulse rate, ≥125/min	18 (6.9)	6 (2.4)	0.02	7 (14.3)	0 (0)	0.02
Laboratory findings						
pH <7.35	5 (1.9)	10 (3.9)	0.2	4 (8.2)	7 (17.1)	0.2
BUN, >10.7 mmol/liter	56 (21.5)	61 (24.0)	0.5	29 (59.2)	24 (58.5)	1.0
Sodium, <130 mEq/liter	9 (3.4)	11 (4.3)	0.6	5 (10.2)	6 (14.2)	0.5
Glucose, >13.9 mmol/liter	16 (6.1)	18 (7.1)	0.7	3 (6.1)	7 (17.1)	0.2
Hematocrit, <30%	4 (1.5)	4 (1.6)	1.0	0 (0)	1 (2.4)	0.5
PO_2, <60 mm Hg (<90%)	57 (21.8)	58 (22.8)	0.8	16 (32.7)	11 (26.8)	0.6
Pleural effusion	103 (39.5)	84 (33.1)	0.1	27 (55.1)	27 (65.9)	0.3
APACHE-II score (mean ± SD)	12.4 ± 4.3	12.5 ± 5.3	0.7	15.5 ± 5.2	16.8 ± 8.2	0.4
PSI score (mean ± SD)	102.4 ± 28.6	104.2 ± 29.3	0.5	144.4 ± 13.0	147.5 ± 14.8	0.3
PSI class			0.4			
I	0 (0)	0 (0)				
II	32 (12.2)	33 (13.0)				
III	61 (23.3)	48 (18.9)				
IV	119 (45.6)	132 (52.0)				
V	49 (18.8)	41 (16.1)				

[a] Unless otherwise noted, data are expressed as numbers (percentages) of patients with the indicated characteristic. BL+M, β-lactam plus macrolide; F, fluoroquinolone; HIV, human immunodeficiency virus; CHF, congestive heart failure; BUN, blood urea nitrogen; NA, not applicable.

than for those receiving monotherapy (8.2% versus 26.8%, respectively; $P = 0.02$). Similarly, the 30-day mortality rate was lower for the combination therapy group than for the monotherapy group, but the difference was of borderline significance (18.4% versus 36.6%, respectively; $P = 0.05$). No differences in the 14-day and 30-day mortality rates were observed for the lower PSI categories. These relationships persisted when we controlled for tachycardia in the multivariate analyses. Among the 12 patients with pneumococcal bacteremia, both 14-day and 30-day mortality rates were higher for the fluoroquinolone monotherapy group than for the β-lactam-plus-macrolide combination group, but the difference was not significant (25% versus 0% [$P = 0.3$ for both comparisons]).

The overall median LOS was significantly longer for the β-lactam-plus-macrolide combination group than for the levofloxacin monotherapy group (6.0 days versus 5.0 days, respectively; $P = 0.01$ [Table 5]). Among patients with severe CAP, the median LOS was 8.0 days for both groups. In the PSI class stratification analysis, the only difference in median LOS between the combination therapy and monotherapy groups was noted for PSI class IV (5.0 days and 4.0 days, respectively; $P = 0.002$). The LOS was not significantly different for the two treatment groups in the other PSI classes.

DISCUSSION

Currently available data suggest that combination therapy for severe CAP confers a significant benefit on patients, par-

TABLE 3. Comparison of causative pathogens for patients receiving empirical combination therapy (β-lactam and macrolide) versus empirical monotherapy (fluoroquinolone)[a]

Characteristic	No. (%) of patients with the indicated characteristic		*P*
	BL+M (*n* = 261)	F (*n* = 254)	
Causative pathogen			0.8
Streptococcus pneumoniae	25 (9.6)	18 (7.1)	
Haemophilus influenzae	9 (3.4)	7 (2.8)	
Haemophilus spp.	13 (5.0)	13 (5.1)	
Moraxella catarrhalis	1 (0.4)	1 (0.4)	
Staphylococcus aureus	8 (3.0)	6 (2.4)	
Klebsiella pneumoniae	1 (0.4)	1 (0.4)	
Pseudomonas aeruginosa	5 (1.9)	4 (1.6)	
Escherichia coli	4 (1.5)	0 (0.4)	
MRSA	2 (0.8)	3 (1.2)	
Streptococcus, not pneumococcus	7 (2.7)	2 (0.8)	
Klebsiella ozaenae	1 (0.4)	0 (0.0)	
Enterobacter cloacae	1 (0.4)	0 (0.0)	
Serratia marcescens	1 (0.4)	1 (0.4)	
Proteus sp.	0 (0.0)	1 (0.4)	
Pseudomonas sp.	1 (0.4)	2 (0.8)	
Presence of bacteremia	16 (6.1)	9 (3.5)	0.2

[a] BL+M, β-lactam plus macrolide; F, fluoroquinolone; MRSA, methicillin-resistant *Staphylococcus aureus*.

TABLE 5. Comparison of LOS for patients receiving empirical combination therapy (β -lactam and macrolide) versus empirical monotherapy (fluoroquinolone)[a]

PSI class (no. in BL+M group, no. in F group)	Median (range) LOS (days)		*P*
	BL+M	F	
Overall (261, 254)	6 (2–63)	5 (2–280)	0.01
I (0, 0)	0	0	NA
II (32, 33)	5 (2–13)	4 (1–39)	0.1
III (61, 48)	4 (1–28)	5 (2–174)	0.5
IV (119, 132)	5 (1–58)	4 (2–46)	0.004
V (49, 41)	8 (3–63)	8 (2–210)	0.6

[a] BL+M, β-lactam plus macrolide; F, fluoroquinolone; NA, not applicable.

ticularly those with bacteremic pneumococcal disease (1, 4, 11, 16, 21, 31, 33, 42, 43). Five observational studies for bacteremic pneumococcal pneumonia have documented a survival advantage associated with dual therapy versus monotherapy (1, 31, 33, 42, 43). Additional observational studies of cohorts of CAP patients with a wider variety of organisms have echoed the previous findings and have identified similar outcome benefits of combination therapy (4, 11, 16, 21). Collectively, these findings across different populations substantiate the likelihood of a significant association between dual therapy and improved outcomes for patients with severe CAP (1, 4, 11, 16, 21, 31, 33, 42, 43).

Despite the increasing evidence in support of combination therapy for patients with severe CAP, previous studies have been unable to identify a specific combination regimen that could improve the outcome, due to the wide range of antibiotic regimens prescribed (1, 4, 11, 16, 21, 31, 33, 42, 43). While these evaluations tended to focus on the combination of an extended-spectrum cephalosporin with a macrolide (4, 11, 16, 31, 33, 42), data comparing outcomes of the two most frequently recommended empirical antibiotic regimens for CAP (dual therapy with an extended-spectrum β-lactam and a macrolide or monotherapy with an antipneumococcal quinolone) for patients with severe CAP are sparse. Furthermore, limited data evaluating the impact of dual therapy versus monotherapy exist for VA patients; it is difficult to generalize the findings of other studies to VA patients because of the vast differences in study populations. Almost all of the clinical studies comparing newer fluoroquinolones with the standard therapeutic CAP regimen were designed to show noninferiority or bioequivalence in order to gain licensing approval; therefore, high-risk patients in PSI class IV or V were usually excluded or poorly represented in these clinical trials (24, 38, 46). It has been well documented that PSI class V patients have an average mortality rate of 27% (15). Hence, it should be noted that no study had evaluated outcomes following β-lactam–macrolide combination therapy versus fluoroquinolone monotherapy for PSI class V VA patients before we undertook this analysis.

This study revealed that both 14-day and 30-day mortality rates were lower among PSI class V patients in the β-lactam-and-azithromycin combination group than in the levofloxacin monotherapy group. This distinction in mortality did not hold for the lower PSI classes. Not surprisingly, given the vastly different outcomes for patients with severe CAP (PSI class V) and nonsevere CAP (PSI classes I to IV), no differences in mortality were detected overall when these two groups were pooled. These findings support the notion that patients with severe CAP may benefit from combination empirical therapy with a β-lactam and azithromycin, and they underscore the importance of examining the effects of treatment for populations at greatest risk for deleterious outcomes, because these

TABLE 4. Comparison of 14-day and 30-day mortality rates for patients receiving empirical combination therapy (β-lactam and macrolide) versus empirical monotherapy (fluoroquinolone)

Group	14-day mortality[a]			30-day mortality		
	BL+M	F	*P*	BL+M	F	*P*
Overall	10/261 (3.8)	14/254 (5.5)	0.4	17/261 (6.5)	27/254 (10.6)	0.1
PSI I	0/0	0/0	NA	0/0	0/0	NA
PSI II	0/32	0/33	NA	0/32	0/33	NA
PSI III	1/61 (1.6)	1/48 (2.1)	0.9	2/61 (3.3)	3/48 (6.3)	0.5
PSI IV	2/119 (1.5)	5/132 (4.2)	0.2	9/119 (6.8)	6/132 (5.0)	0.6
PSI V	4/49 (8.2)	11/41 (26.8)	0.02	9/49 (18.4)	15/41 (36.6)	0.05

[a] Mortality rates are presented as the number of patients dying/total number in the group (percentage). BL+M, β-lactam plus macrolide; F, fluoroquinolone; NA, not applicable.

groups are most dependent on drug exposure for a successful outcome.

Despite the fact that the recommended empirical regimens possess similar spectra of activity, the superiority of β-lactam-and-azithromycin combination therapy over levofloxacin monotherapy for patients with severe CAP may be explained by many factors (41). The macrolides possess immunomodulatory properties that may contribute to the superiority of combination therapy (22, 35, 36). Several studies have demonstrated that macrolides reduce the proinflammatory response to infectious stimuli, including many of the primary cytokines (such as interleukin-1, tumor necrosis factor alpha, interleukin-6, and interleukin-8). Modulation of the immune response may improve patient outcomes by diminishing the proinflammatory complications of sepsis such as secondary organ dysfunction. The immunomodulatory response elicited by macrolides, however, is not global, and macrolides have minimal to no effect on gamma interferon, a key cytokine in the restoration of immune function after sepsis-induced immunoparalysis (22, 35, 36, 45). In contrast, the fluoroquinolones appear to have a more global immunosuppressive effect (8), including significant impairment of gamma interferon (45), and this may contribute to the results observed in this and other studies (1, 4, 11, 16, 21, 31–33, 42, 43). Besides suppressing the release of tumor necrosis factor and other cytokines in response to bacterial stimuli, the macrolides block or downregulate the production of reactive oxygen species, modulate neutrophil function, increase mucociliary clearance, and interfere with biofilm formation and flagellin expression by bacteria (6, 7, 23, 37). Macrolides also reduce the adherence of pneumococci, the major cause of CAP, to respiratory epithelial cells (26). In addition, the use of azithromycin and β-lactam, two agents with different mechanisms of action, may additively or synergistically enhance bacterial killing over that with single-agent therapy (9, 10).

Another notable finding in this study was the shorter LOS for PSI category IV patients in the levofloxacin group compared to the β-lactam–azithromycin combination group. This could be explained by the excellent bioavailability of the oral formulations of fluoroquinolones. Fluoroquinolones have been shown to facilitate an early switch to the oral formulation and discharge from hospital (30). It is noteworthy, however, that the median LOS was comparable between treatment groups among PSI category V patients. While studies have demonstrated early hospital discharge with oral fluoroquinolone therapy, we are not aware of any studies that have demonstrated this for PSI category V patients. It is possible that the critical nature of these patients ' illness negates the potential for early hospital discharge with oral fluoroquinolone therapy. Also, it is possible that the benefits of combination therapy over monotherapy observed in this study may contribute to this observation. Further study is needed to delineate the reasons for the differences in LOS between treatment groups observed in this study.

Among the limitations of our study is the possibility that results for the VA patient population may not be generalizable to other groups. While the optimal study design for comparing treatment regimens is a randomized, controlled trial, such a study would be prohibitively costly and difficult to execute for a variety of reasons (strict inclusion criteria, difficulty in obtaining consent from critically ill patients, etc.). Although this was a retrospective cohort study, the strict inclusion and exclusion criteria used in this study resulted in two groups that were extremely well balanced at baseline. Drawing the study groups from the same time period mitigated any temporal biases introduced by improvements in clinical care standards. Patients on fluoroquinolone monotherapy received 500 mg of levofloxacin every 24 h; the new recommended CAP dose for levofloxacin is 750 mg every 24 h (12, 39). It is not certain whether the same findings would be observed if the optimal levofloxacin dose was evaluated. Also, caution should be exercised in generalizing these results, because they may not be relevant to other members of the fluoroquinolone class. Finally, we did not assess the time to bacterial clearance. The study outcomes were limited to objective end points due to the difficulty in assessing clinical response in the retrospective study design.

In conclusion, this is the first study, to the best of our knowledge, that has specifically examined the outcomes of combination empirical therapy with a β-lactam and azithromycin versus empirical monotherapy with 500 mg of levofloxacin every 24 h for VA patients with severe CAP. The results strongly suggest that combination therapy increases survival for this severely ill patient group. Further study of combination empirical therapy with a β-lactam and azithromycin versus empirical fluoroquinolone monotherapy for patients with severe CAP in a prospective, randomized clinical trial with optimal dosages of fluoroquinolones is warranted based on these results.

ACKNOWLEDGMENTS

This study benefited greatly from the thoughtful editing of Allison Krug.

This study was supported by a grant from Roche Pharmaceuticals. T.P.L. was the principal investigator for this grant.

Roche only provided support to complete the project and was not involved in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation and review of the manuscript. No other conflicts of interest exist for any of the authors.

REFERENCES

1. **Baddour, L. M., V. L. Yu, K. P. Klugman, C. Feldman, A. Ortqvist, J. Rello, A. J. Morris, C. M. Luna, D. R. Snydman, W. C. Ko, M. B. Chedid, D. S. Hui, A. Andremont, and C. C. Chiou.** 2004. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am. J. Respir. Crit. Care Med. **170:**440–444.
2. **Bartlett, J. G., S. F. Dowell, L. A. Mandell, T. M. File, Jr., D. M. Musher, and M. J. Fine.** 2000. Practice guidelines for the management of community-acquired pneumonia in adults. Clin. Infect. Dis. **31:**347–382.
3. **Bartlett, J. G., and L. M. Mundy.** 1995. Community-acquired pneumonia. N. Engl. J. Med. **333:**1618–1624.
4. **Brown, R. B., P. Iannini, P. Gross, and M. Kunkel.** 2003. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. Chest **123:**1503–1511.
5. **Burgess, D. S., and J. S. Lewis II.** 2000. Effect of macrolides as part of initial empiric therapy on medical outcomes for hospitalized patients with community-acquired pneumonia. Clin. Ther. **22:**872–878.
6. **Culić, O., V. Eraković, I. Cepelak, K. Barisić, K. Brajsa, Z. Ferencić, R. Galović, I. Glojnarić, Z. Manojlović, V. Munić, R. Novak-Mircetić, V. Pavicić-Beljak, M. Sucić, M. Veljaca, T. Zanić-Grubisić, and M. J. Parnham.** 2002. Azithromycin modulates neutrophil function and circulating inflammatory mediators in healthy human subjects. Eur. J. Pharmacol. **450:**277–289.
7. **Culić, O., V. Eraković, and M. J. Parnham.** 2001. Anti-inflammatory effects of macrolide antibiotics. Eur. J. Pharmacol. **429:**209–229.
8. **Dalhoff, A., and I. Shalit.** 2003. Immunomodulatory effects of quinolones. Lancet Infect. Dis. **3:**359–371.
9. **Deshpande, L. M., and R. N. Jones.** 2003. Antagonism between penicillin and erythromycin against *Streptococcus pneumoniae*: does it exist? Diagn. Microbiol. Infect. Dis. **46:**223–225.

10. **Djurkovic, S., J. M. Loeffler, and V. A. Fischetti.** 2005. Synergistic killing of *Streptococcus pneumoniae* with the bacteriophage lytic enzyme Cpl-1 and penicillin or gentamicin depends on the level of penicillin resistance. Antimicrob. Agents Chemother. **49:**1225–1228.
11. **Dudas, V., A. Hopefl, R. Jacobs, and B. J. Guglielmo.** 2000. Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: a survey of nonteaching US community hospitals. Ann. Pharmacother. **34:**446–452.
12. **Dunbar, L. M., R. G. Wunderink, M. P. Habib, L. G. Smith, A. M. Tennenberg, M. M. Khashab, B. A. Wiesinger, J. X. Xiang, N. Zadeikis, and J. B. Kahn.** 2003. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clin. Infect. Dis. **37:**752–760.
13. **Dwyer, R., A. Ortqvist, E. Aufwerber, B. Henriques Normark, T. J. Marrie, M. A. Mufson, A. Torres, M. A. Woodhead, M. Alenius, and M. Kalin.** 2006. Addition of a macrolide to a β-lactam in bacteremic pneumococcal pneumonia. Eur. J. Clin. Microbiol. Infect. Dis. **25:**518–521.
14. **Feldman, R. B., D. C. Rhew, J. Y. Wong, R. A. Charles, and M. B. Goetz.** 2003. Azithromycin monotherapy for patients hospitalized with community-acquired pneumonia: a 3 1/2-year experience from a Veterans Affairs hospital. Arch. Intern. Med. **163:**1718–1726.
15. **Fine, M. J., T. E. Auble, D. M. Yealy, B. H. Hanusa, L. A. Weissfeld, D. E. Singer, C. M. Coley, T. J. Marrie, and W. N. Kapoor.** 1997. A prediction rule to identify low-risk patients with community-acquired pneumonia. N. Engl. J. Med. **336:**243–250.
16. **García Vázquez, E., J. Mensa, J. A. Martinez, M. A. Marcos, J. Puig, M. Ortega, and A. Torres.** 2005. Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a beta-lactam agent versus a beta-lactam agent alone. Eur. J. Clin. Microbiol. Infect. Dis. **24:** 190–195.
17. **Gilbert, K., P. P. Gleason, D. E. Singer, T. J. Marrie, C. M. Coley, D. S. Obrosky, J. R. Lave, W. N. Kapoor, and M. J. Fine.** 1998. Variations in antimicrobial use and cost in more than 2,000 patients with community-acquired pneumonia. Am. J. Med. **104:**17–27.
18. **Gleason, P. P., W. N. Kapoor, R. A. Stone, J. R. Lave, D. S. Obrosky, R. Schulz, D. E. Singer, C. M. Coley, T. J. Marrie, and M. J. Fine.** 1997. Medical outcomes and antimicrobial costs with the use of the American Thoracic Society guidelines for outpatients with community-acquired pneumonia. JAMA **278:**32–39.
19. **Harbarth, S., J. Garbino, J. Pugin, J. A. Romand, and D. Pittet.** 2005. Lack of effect of combination antibiotic therapy on mortality in patients with pneumococcal sepsis. Eur. J. Clin. Microbiol. Infect. Dis. **24:**688–690.
20. **Heffelfinger, J. D., S. F. Dowell, J. H. Jorgensen, K. P. Klugman, L. R. Mabry, D. M. Musher, J. F. Plouffe, A. Rakowsky, A. Schuchat, and C. G. Whitney.** 2000. Management of community-acquired pneumonia in the era of pneumococcal resistance: a report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. Arch. Intern. Med. **160:**1399–1408.
21. **Houck, P. M., R. F. MacLehose, M. S. Niederman, and J. K. Lowery.** 2001. Empiric antibiotic therapy and mortality among Medicare pneumonia inpatients in 10 Western states: 1993, 1995, and 1997. Chest **119:**1420–1426.
22. **Ianaro, A., A. Ialenti, P. Maffia, L. Sautebin, L. Rombola, R. Carnuccio, T. Iuvone, F. D'Acquisto, and M. Di Rosa.** 2000. Anti-inflammatory activity of macrolide antibiotics. J. Pharmacol. Exp. Ther. **292:**156–163.
23. **Ivetić Tkalcević, V., B. Bosnjak, B. Hrvacić, M. Bosnar, N. Marjanović, Z. Ferencić, K. Situm, O. Culić, M. J. Parnham, and V. Eraković.** 2006. Anti-inflammatory activity of azithromycin attenuates the effects of lipopolysaccharide administration in mice. Eur. J. Pharmacol. **539:**131–138.
24. **Katz, E., L. S. Larsen, C. M. Fogarty, K. Hamed, J. Song, and S. Choudhri.** 2004. Safety and efficacy of sequential i.v. to p.o. moxifloxacin versus conventional combination therapies for the treatment of community-acquired pneumonia in patients requiring initial i.v. therapy. J. Emerg. Med. **27:**395–405.
25. **Knaus, W. A., E. A. Draper, D. P. Wagner, and J. E. Zimmerman.** 1985. APACHE II: a severity of disease classification system. Crit. Care Med. **13:**818–829.
26. **Lagrou, K., W. E. Peetermans, M. Jorissen, J. Verhaegen, J. Van Damme, and J. Van Eldere.** 2000. Subinhibitory concentrations of erythromycin reduce pneumococcal adherence to respiratory epithelial cells in vitro. J. Antimicrob. Chemother. **46:**717–723.
27. **Lave, J. R., M. J. Fine, S. S. Sankey, B. H. Hanusa, L. A. Weissfeld, and W. N. Kapoor.** 1996. Hospitalized pneumonia. Outcomes, treatment patterns, and costs in urban and rural areas. J. Gen. Intern. Med. **11:**415–421.
28. **Lentino, J. R., and B. Krasnicka.** 2002. Association between initial empirical therapy and decreased length of stay among veteran patients hospitalized with community acquired pneumonia. Int. J. Antimicrob. Agents **19:**61–66.
29. **Mandell, L. A., J. G. Bartlett, S. F. Dowell, T. M. File, Jr., D. M. Musher, and C. Whitney.** 2003. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin. Infect. Dis. **37:**1405–1433.
30. **Marrie, T. J., C. Y. Lau, S. L. Wheeler, C. J. Wong, M. K. Vandervoort, and B. G. Feagan for the CAPITAL Study Investigators.** 2000. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. JAMA **283:**749–755.
31. **Martínez, J. A., J. P. Horcajada, M. Almela, F. Marco, A. Soriano, E. Garcia, M. A. Marco, A. Torres, and J. Mensa.** 2003. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin. Infect. Dis. **36:**389–395.
32. **Mortensen, E. M., M. I. Restrepo, A. Anzueto, and J. Pugh.** 2005. The impact of empiric antimicrobial therapy with a beta-lactam and fluoroquinolone on mortality for patients hospitalized with severe pneumonia. Crit. Care **10:**R8.
33. **Mufson, M. A., and R. J. Stanek.** 1999. Bacteremic pneumococcal pneumonia in one American city: a 20-year longitudinal study, 1978–1997. Am. J. Med. **107:**34S–43S.
34. **Niederman, M. S., L. A. Mandell, A. Anzueto, J. B. Bass, W. A. Broughton, G. D. Campbell, N. Dean, T. File, M. J. Fine, P. A. Gross, F. Martinez, T. J. Marrie, J. F. Plouffe, J. Ramirez, G. A. Sarosi, A. Torres, R. Wilson, and V. L. Yu.** 2001. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am. J. Respir. Crit. Care Med. **163:**1730–1754.
35. **Orman, K. L., and B. K. English.** 2000. Effects of antibiotic class on the macrophage inflammatory response to *Streptococcus pneumoniae*. J. Infect. Dis. **182:**1561–1565.
36. **Parnham, M. J.** 2005. Immunomodulatory effects of antimicrobials in the therapy of respiratory tract infections. Curr. Opin. Infect. Dis. **18:**125–131.
37. **Parnham, M. J., O. Culić, V. Eraković, V. Munić, S. Popović-Grle, K. Barisić, M. Bosnar, K. Brajsa, I. Cepelak, S. Cuzić, I. Glojnarić, Z. Manojlović, R. Novak-Mircetić, K. Oresković, V. Pavicić-Beljak, S. Radosević, and M. Sucić.** 2005. Modulation of neutrophil and inflammation markers in chronic obstructive pulmonary disease by short-term azithromycin treatment. Eur. J. Pharmacol. **517:**132–143.
38. **Querol-Ribelles, J. M., J. M. Tenias, J. M. Querol-Borras, T. Labrador, A. Nieto, D. Gonzalez-Granda, and I. Martinez.** 2005. Levofloxacin versus ceftriaxone plus clarithromycin in the treatment of adults with community-acquired pneumonia requiring hospitalization. Int. J. Antimicrob. Agents **25:**75–83.
39. **Shorr, A. F., M. M. Khashab, J. X. Xiang, A. M. Tennenberg, and J. B. Kahn.** 2006. Levofloxacin 750-mg for 5 days for the treatment of hospitalized Fine Risk Class III/IV community-acquired pneumonia patients. Respir. Med. **100:**2129–2136.
40. **Sue, D. Y.** 1994. Community-acquired pneumonia in adults. West. J. Med. **161:**383–389.
41. **Waterer, G. W., and J. Rello.** 2006. Choosing the right combination therapy in severe community-acquired pneumonia. Crit. Care **10:**115.
42. **Waterer, G. W., G. W. Somes, and R. G. Wunderink.** 2001. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch. Intern. Med. **161:**1837–1842.
43. **Weiss, K., D. E. Low, L. Cortes, A. Beaupre, R. Gauthier, P. Gregoire, M. Legare, F. Nepveu, D. Thibert, C. Tremblay, and J. Tremblay.** 2004. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic *Streptococcus pneumoniae* pneumonia in adults. Can. Respir. J. **11:**589–593.
44. **Whittle, J., C. J. Lin, J. R. Lave, M. J. Fine, K. M. Delaney, D. Z. Joyce, W. W. Young, and W. N. Kapoor.** 1998. Relationship of provider characteristics to outcomes, process, and costs of care for community-acquired pneumonia. Med. Care **36:**977–987.
45. **Williams, A. C., H. F. Galley, A. M. Watt, and N. R. Webster.** 2005. Differential effects of three antibiotics on T helper cell cytokine expression. J. Antimicrob. Chemother. **56:**502–506.
46. **Zervos, M., L. A. Mandell, P. S. Vrooman, C. P. Andrews, A. McIvor, R. H. Abdulla, P. J. de Caprariis, C. A. Knirsch, G. W. Amsden, M. S. Niederman, and H. Lode.** 2004. Comparative efficacies and tolerabilities of intravenous azithromycin plus ceftriaxone and intravenous levofloxacin with step-down oral therapy for hospitalized patients with moderate to severe community-acquired pneumonia. Treat. Respir. Med. **3:**329–336.