Macrolide Antibiotics and Survival in Patients With Acute Lung Injury

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Background: Animal models suggest that immunomodulatory properties of macrolide antibiotics have therapeutic value for patients with acute lung injury (ALI). We investigated the association between receipt of macrolide antibiotics and clinical outcomes in patients with ALI.

Methods: Secondary analysis of multicenter, randomized controlled trial data from the Acute Respiratory Distress Syndrome Network Lisofylline and Respiratory Management of Acute Lung Injury Trial, which collected detailed data regarding antibiotic use among participants with ALI.

Results: Forty-seven of 235 participants (20%) received a macrolide antibiotic within 24 h of trial enrollment. Among patients who received a macrolide, erythromycin was the most common (57%), followed by azithromycin (40%). The median duration of macrolide use after study enrollment was 4 days (interquartile range, 2-8 days). Eleven of the 47 (23%) patients who received macrolides died, compared with 67 of the 188 (36%) who did not receive a macrolide (*P* = .11). Participants administered macrolides were more likely to have pneumonia as an ALI risk factor, were less likely to have nonpulmonary sepsis or to be randomized to low tidal volume ventilation, and had a shorter length of stay prior to trial enrollment. After adjusting for potentially confounding covariates, use of macrolide was associated with lower 180-day mortality (hazard ratio [HR], 0.46; 95% CI, 0.23-0.92; *P* = .028) and shorter time to successful discontinuation of mechanical ventilation (HR, 1.93; 95% CI, 1.18-3.17; *P* = .009). In contrast, fluoroquinolone (n = 90) and cephalosporin antibiotics (n = 93) were not associated with improved outcomes.

Conclusions: Receipt of macrolide antibiotics was associated with improved outcomes in patients with ALI.
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Abbreviations: ALI = acute lung injury; ARDSNet = Acute Respiratory Distress Syndrome Network; HR = hazard ratio; LARMA = Lisofylline and Respiratory Management of Acute Lung Injury; SAPS II = Simplified Acute Physiology II Score

Acute lung injury (ALI) is a syndrome of acute inflammatory pulmonary edema estimated to affect 200,000 people in the United States yearly, with a mortality rate of 30% to 40%.[1] Thus far, only a low tidal volume lung-protective ventilation strategy

has been demonstrated to reduce mortality in ALI.[2] Although numerous pharmacologic interventions for ALI have been studied, none has been shown to reduce mortality.[3-8]

Macrolide antibiotics have pulmonary antiinflammatory actions beyond their antimicrobial activity,[9-11] and have potential clinical benefit in chronic lung diseases such as panbronchiolitis[12] and cystic fibrosis.[13] Animal

models suggest a therapeutic role for macrolide antibiotics in ALI.[14-20]

We sought to investigate the association between macrolide antibiotics and mortality in patients with ALI using data from the Acute Respiratory Distress Syndrome Network (ARDSNet) Lisofylline and Respiratory Management of Acute Lung Injury (LARMA) trial.[8] We hypothesized that use of macrolide antibiotics would be associated with reduced mortality in patients with ALI.

MATERIALS AND METHODS

Data Source

We used deidentified, open-access data from subjects previously enrolled in the ARDSNet LARMA trial, during which antibiotic type and timing was recorded in detail for all participants. Details of LARMA have been published previously.[8] Briefly, participants were enrolled from 21 hospitals across the United States within 36 h of meeting ALI consensus criteria[21] and were randomized via 2×2 factorial design to receive 6 mL or 12 mL/kg tidal volumes (as part of the Respiratory Management of ALI [ARMA] trial) and lisofylline or placebo. All study procedures were approved by the Boston University School of Medicine Institutional Review Board (H-31026) with a data use agreement through the National Heart, Lung and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center.

Subject Characteristics

We recorded prerandomization subject characteristics, including demographics, comorbidities, lung injury risk factors, mechanical ventilation parameters, randomization group, and duration of inpatient care prior to study enrollment. We calculated Simplified Acute Physiology II Score (SAPS II)[22] and Brussels Organ Failure Scores[23] for all subjects.

Antibiotic Exposures

Our primary area of interest was receipt of a macrolide antibiotic (azithromycin, clarithromycin, or erythromycin) within the first 24 h of trial enrollment (ie, the first 60 h of ALI). We chose the 24-h time window in order to reduce immortal time bias that might be associated with macrolide use later in a participant's course.[24]

In order to investigate a potential class effect of any antibiotic effective against atypical pathogens, we performed a secondary analysis investigating the association between receipt of a fluoroquinolone and survival. We performed additional analyses for any antibiotic coadministered in >50% of patients who received a macrolide.

Outcomes

Our a priori primary outcome was multivariable-adjusted 180-day survival. As a secondary outcome, we evaluated time to successful discontinuation of mechanical ventilation. Time to successful discontinuation of mechanical ventilation, an analog of ventilator-free days,[25] was defined as the time to achieve 48 h of unassisted breathing, censored at day 28. Because death biases toward fewer ventilator days, participants who died prior to day 28 were assigned as having 28 ventilator days.[25]

Statistical Methods

We analyzed differences in continuous and categorical variables with Wilcoxon rank sum and Fisher exact tests, respectively. Given the likelihood of imbalanced covariates among antibiotic exposure groups, we used multivariable-adjusted Cox proportional hazards models as our a priori primary analysis to evaluate adjusted differences in survival and time to successful discontinuation of ventilation among antibiotic groups. We included the a-priori-defined covariates age and SAPS II, and covariates imbalanced with $P < .10$ among antibiotic exposure groups. Stepwise regression was used to select among collinear covariates for inclusion in the multivariable models (eg, between durations of hospital stay and ICU stay prior to trial enrollment). We evaluated the proportional hazards assumption with log-log plots and tests of interactions among time, macrolide exposure, and survival. We used unadjusted and adjusted Kaplan-Meier survival plots to visually demonstrate survival differences among the antibiotic groups.

As a sensitivity analysis, we used propensity scores to adjust for potential confounding by indication for each antibiotic in Cox proportional hazards models. Nonparsimonious propensity scores for use of each antibiotic were calculated using multivariable logistic regression models, including all measured covariates with <20% missing data.[26,27] Propensity score model discrimination was measured via the area under the receiver operating curve (C statistic).

Because macrolides are often used to treat pneumonia, we evaluated the interaction between pneumonia diagnosis and the association between macrolide and mortality. In addition, we tested for interaction between randomization to the 6 mL/kg or 12 mL/kg group and the association between macrolide and mortality. We chose an α level of 0.05. SAS software, version 9.1 was used for all statistical analyses; survival plots were generated with PASW statistics 18.0.

RESULTS

The characteristics of the 235 study participants stratified by macrolide exposure are shown in Table 1. Analogous results for fluoroquinolone use are shown in Table 2.

An antibiotic was administered to 232 of 235 trial participants (99%) within 24 h of enrollment. Macrolide antibiotics were used in 47 trial participants (20%). The most common macrolide received was erythromycin (n = 27, 57%), followed by azithromycin (n = 19, 40%); one participant received clarithromycin. The median duration of macrolide use after trial enrollment was 4 days (interquartile range, 2-8 days).

Seventy-eight participants in the trial died prior to the 180-day outcome assessment: 11 of 47 (23%) who received macrolides died, compared with 67 of the 188 (36%) who did not receive macrolide (P = .11) (Fig 1). After adjustment for confounding covariates, mortality was significantly lower in participants who did receive macrolide antibiotics compared with those who did not (Fig 2, Table 3). In addition, the time to successful discontinuation of mechanical ventilation was shorter in participants given macrolides, compared with participants not receiving macrolides (adjusted hazard ratio [HR] for successful ventilator

Table 1—Baseline Characteristics of Study Cohort Stratified by Macrolide Exposure

Variable	Macrolide (n = 47)	No Macrolide (n = 188)	P Value
Age, y	51 ± 16	51 ± 17	.88
Sex, male	30 (64)	115 (62)	.87
Race, white	36 (77)	143 (76)	.47
BMI, kg/m² (n = 228)	27.5 ± 7.3	28.3 ± 7.6	.57
Primary ALI risk factor			
Pneumonia	36 (77)	48 (26)	< .001[a]
Nonpulmonary sepsis	4 (8.5)	54 (29)	.004[a]
Aspiration	12 (13)	26 (18)	.47
Trauma	5 (6)	17 (12)	.17
Multiple transfusions	0	6 (4)	.18
Other	8 (10)	19 (12)	.83
SAPS II	45.8 ± 14.5	48.0 ± 15.1	.61
Brussels Organ Failure Score	1.72 ± 0.85	1.86 ± 1.06	.60
Comorbidities			
Diabetes	10 (21)	32 (17)	.42
AIDS	4 (9)	10 (5)	.49
Metastatic or hematologic malignancy	2 (4)	12 (6)	.74
End-stage renal failure/dialysis	0	4 (2)	.59
Radiographic lung injury score (n = 232)	3.7 ± 0.6	3.7 ± 0.6	…
Tidal volume, mg/kg of IBW (n = 157)	9.7 ± 2.0	10.4 ± 2.0	.14
Pao_2/Fio_2 (n = 221)	147 ± 69	141 ± 54	.96
PEEP, cm H_2O	10.2 ± 5.2	8.7 ± 3.8	.11
Pplat, cm H_2O (n = 185)	31 ± 8.1	30 ± 8.8	.52
Peak pressure, cm H_2O (n = 213)	38 ± 11	37 ± 10	.59
$Paco_2$, mm Hg (n = 221)	36 ± 9.5	36 ± 8.5	.83
Arterial pH	7.41 ± 0.08	7.40 ± 0.07	.58
Minute ventilation, L/min	13 ± 4.5	13 ± 3.8	.74
Duration of intubation prior to enrollment, median (IQR), d	1 (1-1)	1 (1-2)	.13
Duration of ICU stay prior to enrollment, median (IQR), d	1 (0-1)	1 (1-2)	.0004[a]
Duration of hospitalization prior to enrollment, median (IQR), d	1 (1-2)	2 (1-5)	.01[a]
Randomized to low tidal volume	20 (43)	115 (61)	.03[a]
Randomized to lisofylline	23 (49)	93 (49)	1.0

Continuous variables are presented as mean ± SD and categorical variables are presented as No. (%) unless indicated otherwise. N = 235, unless otherwise noted. ALI = acute lung injury; IBW = ideal body weight; IQR = interquartile range; PEEP = positive end-expiratory pressure; Pplat = plateau pressure; SAPS II = Simplified Acute Physiology II Score.
[a]P < .1 and consideration for inclusion in multivariable model.

discontinuation, 1.93; 95% CI, 1.18-3.17; P = .009) (Fig 3). We did not identify mortality differences between participants who received fluoroquinolones vs those who did not (Table 3). Cephalosporins (n = 93) were coadministered to 24 patients (51%) receiving a macrolide, but administration of cephalosporins was not associated with mortality (Table 3). We did not identify a statistically significant interaction between macrolides and mortality for pneumonia status (HR with pneumonia, 0.70 [n = 84] vs HR without pneumonia, 0.16 [n = 151]; P for interaction = .19) or tidal volume randomization group (HR, 6 mL/kg 0.26 [n = 135] vs HR, 12 mL/kg 0.66 [n = 100]; P for interaction = .18).

Discussion

The analysis suggests an association between macrolide antibiotic use and improved outcomes in ALI.

We observed increased survival and decreased time to successful discontinuation of mechanical ventilation associated with receipt of a macrolide early during the course of ALI. Our analyses did not demonstrate an association between fluoroquinolone or cephalosporin use and ALI survival. These findings suggest that macrolide antibiotics hold promise as a potential therapy early in the course of ALI.

We identified several factors associated with macrolide use. Patients with pneumonia as an ALI risk factor were more likely to receive macrolides. In contrast, patients with nonpulmonary sepsis were less likely to receive macrolides. Patients with greater ICU length of stay prior to ALI onset were also less likely to receive a macrolide. We speculate that suspected nosocomial infections were less likely to be treated with a macrolide. Patients who received a macrolide were less likely to be randomized to the low tidal volume strategy previously shown to result in lower mortality,[2] an observation that makes the

Variable	Fluroquinolone (n = 90)	No Fluoroquinolone (n = 145)	P Value
Age, y	51 ± 17	51 ± 17	.98
Sex, male	47 (52)	98 (68)	.02[a]
Race, white	71 (79)	108 (75)	.53
BMI, kg/m²	28.6 ± 8.3	27.9 ± 7.1	.88
Primary ALI risk factor			
Pneumonia	39 (43)	45 (31)	.07[a]
Sepsis	25 (28)	33 (23)	.43
Aspiration	12 (13)	26 (18)	.47
Trauma	5 (6)	17 (12)	.17
Multiple transfusions	1 (1)	5 (3.5)	.41
Other	8 (9)	19 (13)	.40
SAPS II	50.7 ± 15.7	45.6 ± 14.2	.02[a]
Brussels Organ Failure Score	2.0 ± 1.11	1.70 ± 0.94	.05[a]
Comorbidities			
Diabetes	15 (17)	27 (19)	.73
AIDS	5 (6)	9 (6)	1.0
Metastatic or hematologic malignancy	7 (8)	7 (5)	.40
End-stage renal failure/dialysis	3 (3)	1 (0.7)	.16
Radiographic lung injury score	3.71 ± 0.55	3.70 ± 0.61	
Tidal volume, mg/kg of IBW	10.4 ± 2	10 ± 2	.19
Pao_2/Fio_2	144 ± 73	146 ± 62	.36
PEEP, cm H_2O	8.8 ± 4.3	9.1 ± 4.0	.38
Pplat, cm H_2O	30 ± 10	30 ± 7.8	.48
Peak pressure, cm H_2O	37 ± 12	36.8 ± 8.8	.85
$Paco_2$, mm Hg	35 ± 10	37 ± 8.1	.14
Arterial pH	7.39 ± 0.09	7.41 ± 0.07	.31
Minute ventilation, L/min	13.5 ± 4.2	12.7 ± 3.72	.18
Duration of intubation prior to enrollment, median (IQR), d	1 (0-1)	1 (1-2)	.02[a]
Duration of ICU stay prior to enrollment, median (IQR), d	1 (1-2)	1 (1-2)	.05[a]
Duration of hospitalization prior to enrollment, median (IQR), d	2 (1-5)	2 (1-4)	.32
Randomized to low tidal volume	52 (58)	83 (57)	1.0
Randomized to lisofylline	47 (52)	69 (48)	.51

Continuous variables are presented as mean ± SD and categorical variables are presented as No. (%) unless indicated otherwise. See Table 1 legend for expansion of abbreviations.

[a]$P < .1$ and consideration for inclusion in multivariable model.

improved outcomes associated with the use of macrolides even more striking. We did not find evidence to support differences in the association between mac-
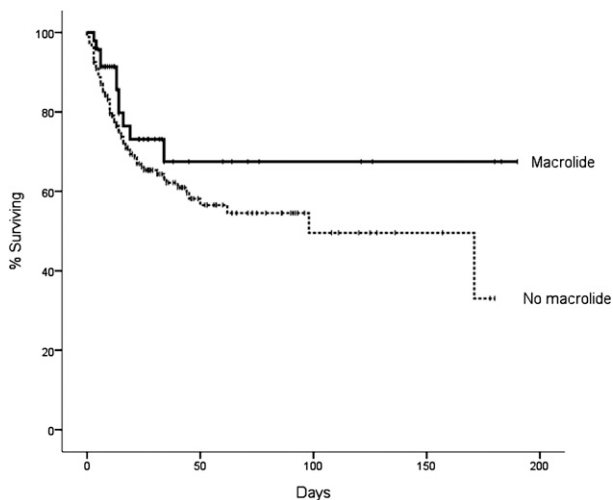

FIGURE 1. Unadjusted Kaplan-Meier survival plots for the association between macrolide use and 180-day mortality. Log rank test, $P = .15$.

rolides and improved outcomes based on whether patients were randomized to low tidal volume or whether patients had pneumonia as an ALI risk factor. After adjusting for observed imbalances in clinical characteristics based on macrolide use using both multivariable-adjusted and propensity-score-adjusted regression models, we observed a significant association between use of macrolides and important clinical outcomes, including survival and successful discontinuation of mechanical ventilation.

Several mechanisms may explain a potential benefit of macrolides in ALI. Macrolide antibiotics may treat bacterial organisms not covered by other antibiotics, such as *Legionella* species. However, broader-spectrum antibiotic coverage is a less plausible explanation because similar associations with survival were not seen with fluoroquinolone antibiotics, which have similar atypical pathogen activity. Alternatively, macrolide antibiotics have been shown to have antiinflammatory effects, which may decrease the inflammation associated with ALI.[28] These antiinflammatory effects may be responsible for the improved outcomes seen with
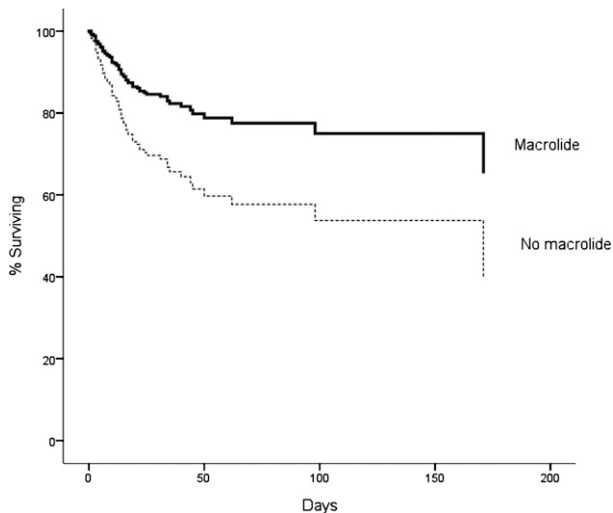
FIGURE 2. Survival curves for the association between macrolide use and 180-day mortality from the Cox proportional hazards model, adjusted for age, Simplified Acute Physiology II Score, duration of ICU stay prior to study enrollment, tidal volume randomization group, presence of pneumonia, and presence of sepsis. Use of a macrolide antibiotic was associated with decreased mortality (relative risk, 0.46; 95% CI, 0.23-0.92; *P* = .028).

the use of macrolide therapy in community-acquired pneumonia,[11] ventilator-associated pneumonia,[29] diffuse panbronchiolitis,[12] and cystic fibrosis.[13] Specifically, the pleiotropic antiinflammatory activities of macrolides include attenuation of pulmonary epithelial cell nuclear factor-κB activity,[30] decreased survival[31] and oxidative burst[32] of activated neutrophils, reduced endotoxin-induced goblet cell hypersecretion,[18] and inhibition of immune-complex-induced lung injury.[17] The potential therapeutic value of the antiinflammatory effects of macrolides is supported by observations in murine models of ALI caused by endotoxin,[16,19] influenza,[14] or bleomycin,[15,20] which have demonstrated less severe injury and increased survival with macrolide treatment.

Our study has several limitations. First, we investigated macrolide use within 24 h of trial enrollment and did not have information on medication use prior to trial enrollment. Whether macrolide use later in ALI is associated with benefit is unclear. Second, our study was underpowered to detect differences in interaction analyses, and larger studies are needed to confirm our findings. Whereas the number of patients who received macrolides was relatively small in the LARMA trial, the ARDSNet open-access database is uniquely suited to investigate the association between macrolide use and outcomes of patients with ALI because of the specific inclusion of patients with ALI and detailed covariate information. In contrast, administrative data sets that rely on *International Classification of Diseases, Ninth Revision* codes do not reliably identify patients with ALI/ARDS.[33] Third, it is possible that residual confounding by indication for macrolide or by unmeasured covariates may have biased our results if patients who received a macrolide were less ill than those not receiving macrolides. However, the lack of any survival benefit associated with other antibiotics of similar spectrum (eg, fluoroquinolones) and the similar baseline SAPS II and number of organ failures in the macrolide and nonmacrolide groups decrease the likelihood of strong confounding by indication. Finally, the ARDSNet LARMA data set used for this study is now more than 10 years old; whether changes in ALI practice patterns over time (such as the use of lung protective ventilation) would modify the potential benefit of macrolides is unknown. However, we did not detect an interaction between lung protective ventilation and macrolides that influenced mortality.

Conclusions

In conclusion, this analysis suggests a novel association between macrolide use and increased survival in patients with ALI. Further studies to investigate potential therapeutic benefits for macrolides in ALI are warranted.

Table 3—*Cox Proportional Hazards Model Results for Antibiotics and Mortality*

Model	Macrolide (n = 47)			Fluoroquinolone (n = 90)			Cephalosporin (n = 93)		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Unadjusted (n = 235)	0.63	0.33-1.19	.15	1.18	0.75-1.85	.48	0.86	0.54-1.36	.51
Multivariable adjusted (n = 235)	0.46	0.23-0.92	.028[a]	0.97	0.61-1.55	.90[b]	0.76	0.47-1.25	.28[c]
Propensity adjusted[d] (n = 193)	0.37	0.16-0.88	.024	0.84	0.45-1.57	.58	0.93	0.53-1.63	.80

See Table 1 legend for expansion of abbreviations.
[a]Adjusted for age, SAPS II, and covariates imbalanced with *P* < .1: duration of ICU stay prior to study enrollment, tidal volume randomization group, presence of pneumonia, and presence of sepsis.
[b]Adjusted for age, SAPS II, and covariates imbalanced with *P* < .1: sex, duration of intubation prior to study enrollment, and presence of pneumonia.
[c]Adjusted for age, SAPS II, and covariates imbalanced with *P* < .1: duration of hospitalization prior to study enrollment, and presence of trauma.
[d]C statistics for propensity score regression models were as follows: macrolide 0.87, fluoroquinolone 0.80, cephalosporin 0.67.
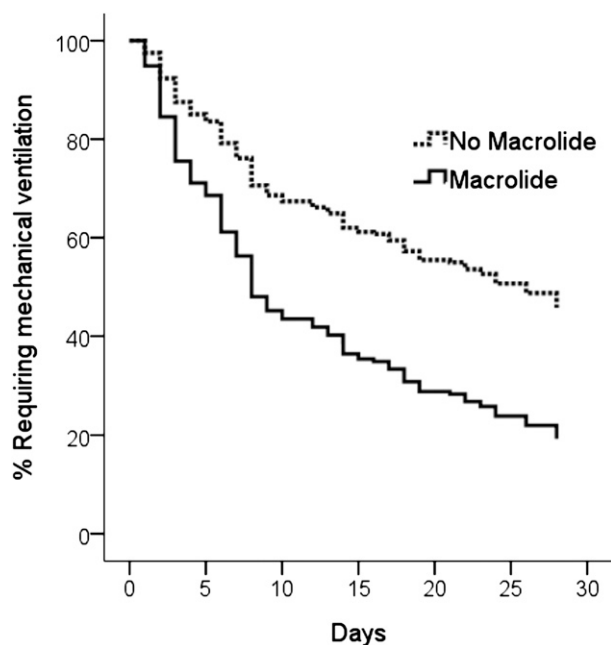
FIGURE 3. Survival curves for the association between macrolide use and successful discontinuation of mechanical ventilation at 28 days. Cox proportional hazards model adjusted for age, Simplified Acute Physiology II Score, duration of ICU stay prior to study enrollment, tidal volume randomization group, presence of pneumonia, and presence of sepsis. Use of a macrolide antibiotic was associated with a significant increase in the likelihood of achieving successful discontinuation of mechanical ventilation (hazard ratio, 1.93; 95% CI, 1.18-3.17; P = .009).

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