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Macrolide-based regimens in absence of bacterial co-infection in critically ill H1N1 patients with primary viral pneumonia

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Abstract *Purpose:* To determine whether macrolide-based treatment is associated with mortality in critically ill H1N1 patients with primary viral pneumonia. *Methods:* Secondary analysis of a prospective, observational, multicenter study conducted across 148 Intensive Care Units (ICU) in Spain. *Results:* Primary viral pneumonia was present in 733 ICU patients with pandemic influenza A (H1N1) virus infection with severe respiratory failure. Macrolide-based treatment was administered to 190 (25.9 %) patients. Patients who received macrolides had chronic obstructive pulmonary disease more often, lower severity on admission (APACHE II score on ICU admission (13.1 ± 6.8 vs. 14.4 ± 7.4 points, $p < 0.05$), and multiple organ dysfunction syndrome less often (23.4 vs. 30.1 %, $p < 0.05$). Length of ICU stay in survivors was not significantly different in patients who received macrolides compared to patients who did not (10 (IQR 4–20) vs. 10 (IQR 5–20), $p = 0.9$). ICU mortality was 24.1 % ($n = 177$). Patients with macrolide-based treatment had lower ICU mortality in the univariate analysis (19.2 vs. 28.1 %, $p = 0.02$); however, a propensity score analysis showed no effect of macrolide-based treatment on ICU mortality (OR = 0.87; 95 % CI 0.55–1.37, $p = 0.5$). Moreover, the

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sensitivity analysis revealed very similar results (OR = 0.91; 95 % CI 0.58–1.44, $p = 0.7$). A separate analysis of patients under mechanical ventilation yielded similar results (OR = 0.77; 95 % CI 0.44–1.35, $p = 0.4$). *Conclusion:* Our results suggest that macrolide-based treatment was not associated with improved survival in critically ill H1N1 patients with primary viral pneumonia.

Introduction

Pandemic (H1N1)v influenza A infection often presents with severe acute respiratory symptoms in hospitalized patients [1]. What made this infection different from the normal seasonal varieties of influenza was the high fatality rates despite aggressive therapy. The principal clinical syndrome leading to hospitalization and intensive care was diffuse viral pneumonitis associated with severe hypoxemia, acute respiratory distress syndrome (ARDS), and sometimes shock and renal failure [2–5].

As early as June 2009, Perez-Padilla et al. [11] reported 38 % mortality in Mexico, and high rates were also reported in Spain (25 %), Canada (17.3 %), and Australia and New Zealand (14.3 %) [6–8]. Several recommendations have been based on the literature published during this time, mainly related to the identification of risk factors such as community-acquired respiratory co-infection (CARC) [9] and/or obesity [10].

There is often an abnormal inflammatory pathway that can cause irreversible damage to the lung tissue. No survival benefit has been found for systemic corticosteroids [11, 12], and early oseltamivir administration [13, 14] seems the only feasible option. Immune modulation concomitant to antibiotic therapy improves outcome in bacterial community-acquired pneumonia (CAP) [15]. The impact of potential adjuncts to antimicrobials on inflammation involves modulation of leukocyte biology, altered antigen-presenting cell function, and changes in epithelial and endothelial cells [16].

The main objective of this study was to determine whether a macrolide-based regimen was associated with mortality in critically ill H1N1 patients with primary viral pneumonia.

Materials and methods

We conducted a secondary analysis of a prospective, observational cohort study of patients in 148 intensive care units (ICU) in Spain. Data were obtained from a voluntary registry created by the Spanish Society of Intensive Care Medicine (SEMICYUC), the Spanish Network for Research on Infectious Disease (REIPI), and the Spanish Biomedical Research Network on Respiratory Diseases (CIBERES). The Joan XXIII University Hospital Ethics Committee approved the study (*IRB NEUMAGRIP/11809*) and waived the requirement for informed consent because patient anonymity was guaranteed and the study was observational and formed part of an emergency public health response [6].

Data were reported by the attending physician after reviewing medical charts and radiological and laboratory records. We analyzed data from all consecutive patients within the cohort diagnosed with pandemic (H1N1)v influenza A infection in two periods: the 2009 pandemic (H1N1)v infection period between epidemiological weeks 23–52 of 2009 and the post-pandemic influenza (H1N1)v infection period between epidemiological weeks 50–52 of 2010 and weeks 1–9 of 2011. Children under 15 years old were not included in the registry. A/H1N1 infection was confirmed by real-time reverse-transcription-polymerase chain reaction (RT-PCR) on either nasopharyngeal swab samples or tracheal secretions ordered by the attending physicians on admission to the ICU. RT-PCR was performed in each institution or in a centralized reference laboratory when local resources were not available. RT-PCR methods and further details are described elsewhere [6]. A confirmed case was defined as acute respiratory illness with laboratory-confirmed A/H1N1. Only confirmed cases were included in the current report.

The ICU admission criteria and treatment decisions for all patients, including determination of the need for intubation and type of antibiotic or antiviral therapy administered, were made at the discretion of the attending physician and not standardized. Septic shock and multiple organ dysfunction score (MODS) were defined following the criteria of the American College of Chest Physicians and the Society of Critical Care Medicine [17].

Systemic corticosteroids were administered when patients developed shock (hydrocortisone) or as adjuvant treatment for pneumonia (methylprednisolone). Attending physicians decided whether to administer oral oseltamivir (150 or 300 mg/24 h) or intravenous zanamivir (600 mg/12 h).

Primary viral pneumonia was defined as unequivocal alveolar opacities involving two or more lobes in patients presenting acute respiratory distress and negative respiratory and blood bacterial cultures during the acute phase of influenza virus infection. Immunosuppression was defined as any primary immunodeficiency or

immunodeficiency secondary to HIV infection (the CD4 count was not recorded in HIV+ patients), active malignancies, radiation treatment, cytotoxic drugs, steroid drugs (daily doses > 40 mg of prednisolone or the equivalent for >2 weeks), immunological disease, or solid organ transplant. Hematological disease was defined as acute lymphoblastic leukemia, acute myeloblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, myeloma, graft-versus-host disease, or postbone marrow transplantation. Obese patients were defined as those with a body mass index (BMI) > 30 kg/m^2 [10]. Smoking history was not recorded. The diagnosis and management of all patients were based on standardized guidelines [18, 19] and specific protocols published by the Spanish Ministry of Health [20]. Blood samples for cultures and serologic studies were routinely collected at ICU admission. Bronchoalveolar lavage was not performed because of the high risk of generating aerosols. Pleural effusion cultures were obtained in patients with documented pleural effusion. Bacterial identification and susceptibility testing were performed by standard methods based on local guidelines. An organism was considered the definitive etiologic agent [21] only if it could be isolated from blood or pleural fluid. Other microorganisms isolated from quantitative endotracheal aspirate (ETA) were considered "probable" pathogens [21]. Acute kidney injury and its stages were diagnosed according to the glomerular filtration rate (GFR) criteria of the current Acute Kidney Injury Network definitions [22]. Continuous renal replacement therapy (CRRT) in the course of acute kidney injury was initiated when indicated for pulmonary edema, oliguria (defined as urine output <0.5 mL/kg body weight per hour for >6 h), metabolic acidosis or hyperkalemia not responding to conventional treatment, or uremia (defined as urea nitrogen >100 mg/dL). CRRT was available 24 h a day, and no patient requiring CRRT was denied treatment due to likely futility.

Statistical analysis

Discrete variables were expressed as counts (percentage) and continuous variables as mean ± standard deviation (SD) or medians with 25th to 75th interquartile range (IQR). For the demographic and clinical characteristics of the patients, differences between groups were assessed using the chi-square test or Fisher's exact test for categorical variables and Student's t test or the Mann–Whitney U test for continuous variables when appropriate. Multivariable stepwise logistic regression analysis was used to assess the impact of explanatory variables on outcome (ICU mortality). To avoid spurious associations, only variables with a relationship in univariate analysis ($p \leq 0.1$) or a potential plausible relationship with

outcome were entered in the logistic regression models. In addition, the effectiveness of the macrolides on ICU mortality was further estimated using propensity scores. Propensity score analysis aims to balance observed covariates between treated and untreated patients from the study to mimic what happens in a randomized study [23], thus creating a quasi-randomized experiment from a non-randomized observational study. In our study, propensity scores were estimated by fitting a logistic regression. The covariates included in the propensity score model were those with a potential impact on outcome measured previous to macrolide treatment: age, APACHE II score, gender, chronic obstructive pulmonary disease (COPD), asthma, cardiac heart failure, chronic renal failure, hematological disease, pregnancy, obesity, diabetes, immunosuppression, and empiric oseltamivir treatment. Propensity score quintiles were derived, and boxplots of the estimated propensity scores for treated and untreated patients within each quintile of the propensity scores were plotted to assess the validity of the analysis. Finally, we fitted a logistic model for outcome including as covariates the propensity score quintiles and treatment. Results are presented as odds ratios (OR) and 95 % confidence intervals (CI). Additionally, a sensitivity analysis was conducted including the post-treatment variables in the propensity score analysis. These variables were invasive mechanical ventilation (MV), septic shock, multiorgan dysfunction/failure, corticosteroid use, and CRRT. For all analyses, p values <0.05 were considered significant. We used SPSS for Windows 20.0 (IBM SPSS Statistics, Chicago, IL, US) for all analyses.

Results

Primary viral pneumonia was present in 733 patients (440 (60.3 %) male) with RT-PCR-confirmed pandemic influenza A (H1N1) virus infection and severe respiratory failure in ICUs in 148 hospitals in Spain. Patients' median age was 46 (IQR 35–55) years, and 669 (91.3 %) patients were aged below 65 years. The mean APACHE II score was 14.3 ± 7.3. A total of 509 (69.9 %) patients had comorbidities, including obesity [$n = 279$ (38.3 %)], COPD [$n = 95$ (13.0 %)], and diabetes mellitus [$n = 88$ (12.1 %)].

Macrolides were administered in 190 (25.9 %) patients; in 188 (98.9 %) of these, macrolides were administered in combination therapy. Clarithromycin was administered in 99 patients (52.1 %), azithromycin in 90 (47.4 %), and erythromycin in 1 patient (0.5 %). In the 543 patients who did not receive macrolide-based regimens, 451 patients (83.1 %) received double combination therapy and 57 (10.5 %) received triple combination therapy. In the patients for whom data was available

($n = 697$), the duration of antibiotic therapy did not differ significantly between patients administered macrolide-based regimens and those administered antibiotics without macrolides (9.4 ± 4.1 vs. 9.9 ± 4.1 days, $p = 0.1$). Patients who received macrolides had lower APACHE II scores on ICU admission (13.1 ± 6.8 vs. 14.4 ± 7.4 points, $p < 0.05$). Macrolides were administered more often in pregnant women ($p = 0.0001$) and COPD patients ($p = 0.03$). The mean interval between symptom onset and antibiotic administration was similar between patients who received macrolides and those who did not (5.1 ± 2.3 vs. 5.3 ± 3.3 days, $p = 0.5$). Table 1 shows the demographic data and clinical characteristics of patients with pandemic (H1N1)v influenza A infection treated with macrolide-based regimens versus those treated without macrolide-based regimens. MODS developed less frequently in patients who received macrolide-based treatment than in those who did not (23.4 vs. 30.1 %, $p < 0.05$) (Table 2). Length of ICU stay in survivors did not differ between patients who received

macrolide-based regimens and those who did not (10 (IQR 4–20) vs. 10 (IQR 5–20), $p = 0.9$).

The overall ICU mortality was 24.1 % ($n = 177$). The use of macrolides was associated with lower ICU mortality in the univariate analysis (19.2 vs. 28.1 %, $p = 0.02$). Table 3 shows details of risk factors for ICU mortality. Briefly, chronic renal disease, hematological disease, and immunosuppression were comorbid conditions significantly associated with higher ICU mortality; in addition, MV, septic shock, MODS, corticosteroids, and CRRT were more frequent in patients who died. A logistic regression analysis adjusted for severity (APACHE) and potential confounding factors (COPD, congestive heart failure, pregnancy, chronic renal failure, morbid obesity, immunosuppression and hematological disease) found the use of macrolides was not significantly associated with lower ICU mortality rate (OR = 0.89; 95 % CI 0.53–1.49, $p = 0.6$).When the analysis was done on the subgroup of patients receiving MV, similar results were obtained (OR = 0.77; 95 % CI 0.44–1.35, $p = 0.4$). The propensity score analysis found no effect of macrolide treatment on outcome (OR = 0.87; 95 % CI 0.55–1.37, $p = 0.5$), and the sensitivity analysis revealed a very similar result (OR = 0.91; 95 % CI 0.58–1.44, $p = 0.7$). Moreover, the overlapping of the propensity scores for treated and untreated patients within each propensity score quintile reinforced the validity of the propensity score analysis (Fig. 1). Finally, the length of the ICU stay in survivors was similar in patients who received macrolides and in those who did not (10 (IQR, 4–20) vs. 10(IQR 5–20), $p = 0.6$).

Table 1 Comparison of demographic and clinical characteristics between patients with pandemic 2009 influenza A (H1N1) virus infection who received macrolides and those who received no macrolides

Variables	No macrolide-based treatment $N = 543$	Macrolide-based treatment $N = 190$	p
Age, years Mean (SD)	46 ± 13.9	44 ± 14.0	0.2
Male sex n (%)	331 (61.3)	109 (57.4)	0.3
APACHE II score Mean (SD)	14.4 ± 7.4	13.1 ± 6.8	0.04
COPD n (%)	62 (11.5)	33 (17.5)	0.03
Asthma n (%)	41 (7.6)	12 (6.3)	0.5
Chronic heart failure n (%)	31 (5.8)	8 (4.2)	0.4
Chronic renal disease n (%)	30 (5.6)	6 (3.2)	0.1
Hematological disease n (%)	58 (10.8)	8 (4.2)	0.007
Pregnancy n (%)	20 (3.7)	20 (10.6)	0.0001
Obesity n (%)	205 (38.0)	74 (39.2)	0.7
Diabetes n (%)	64 (11.9)	24 (12.7)	0.7
Autoimmune disease n (%)	24 (4.5)	6 (3.2)	0.5
Immunosuppression n (%)	61 (11.1)	58 (33)	0.0001

APACHE acute physiology and chronic health evaluation, *COPD* chronic obstructive pulmonary disease

Table 2 Comparison of clinical characteristics between patients with primary viral pneumonia caused by pandemic 2009 influenza A (H1N1) virus infection who received macrolides and those who received no macrolides

Variables	No macrolide-based treatment $N = 543$	Macrolide-based treatment $N = 190$	p
Invasive mechanical ventilation n (%)	357 (66.7)	118 (62.1)	0.2
Septic shock n (%)	268 (50.5)	82 (43.4)	0.09
MODS n (%)	341 (63.4)	104 (55.0)	0.04
CRRT n (%)	58 (10.8)	14 (7.4)	0.2
Empirical oseltamivir n (%)	555 (99.6)	175 (97.7)	0.01
Corticosteroids n (%)	216 (39.2)	91 (53.2)	0.001

MODS multiple organ dysfunction syndrome, *CRRT* continuous renal replacement therapy

Table 3 Risk factors for ICU mortality among patients with primary viral pneumonia caused by pandemic 2009 influenza A (H1N1) virus infection

Variables	Alive N = 564	Dead N = 181	p
Age. years Mean (SD)	46.6 ± 14.2	48.9 ± 14.9	0.01
Male sex n (%)	323 (58.4)	117 (66.1)	0.04
APACHE II score Mean (SD)	12.4 ± 6.0	19.5 ± 8.6	0.0001
COPD n (%)	66 (12.0)	29 (16.5)	0.1
Asthma n (%)	42 (7.6)	11 (6.3)	0.4
Chronic heart failure n (%)	25 (4.5)	14 (8.0)	0.08
Chronic renal disease n (%)	19 (3.4)	17 (9.7)	0.002
Hematological disease n (%)	29 (5.3)	37 (21.0)	0.0001
Immunosuppression n (%)	29 (5.3)	37 (21.0)	0.0001
Pregnancy n (%)	32 (5.8)	8 (4.5)	0.5
Obesity n (%)	212 (38.4)	67 (37.1)	0.9
Diabetes n (%)	67 (12.1)	21 (11.9)	0.9
Invasive mechanical ventilation n (%)	309 (56.4)	166 (93.8)	0.0001
Shock n (%)	220 (40.4)	130 (74.3)	0.0001
MODS n (%)	296 (53.6)	149 (85.1)	0.0001
Corticosteroids n (%)	216 (39.8)	91 (53.8)	0.001
CRRT n (%)	21 (3.8)	51 (29.1)	0.0001
Oseltamivir n (%)	547 (99.6)	173 (98.3)	0.09

APACHE acute physiology and chronic health evaluation, *COPD* chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *MODS* multiple organ dysfunction syndrome, *CRRT* continuous renal replacement therapy

Discussion

This secondary analysis of a multicenter prospective observational cohort study in ICU patients with pandemic (H1N1)v influenza A infection suggests that the use of macrolides does not result in a reduction in mortality in patients with primary viral pneumonia.

Several studies have found better outcomes in patients with CAP administered combinations of antibiotics [24–26] and also, more specifically, in patients with CAP administered combinations of macrolides with other antibiotics [27–30]. Restrepo et al. [31] found that the use of macrolides in combination therapy improved outcomes in patients with CAP and severe sepsis. Tessmer et al. [32] analyzed a large cohort of patients with CAP and reported better 14-day outcome for patients with high CRB65 (confusion, respiratory rate, blood pressure and age over 65 years) risk classes receiving beta-lactam/macrolide compared to those receiving beta-lactam alone. More recently, our group analyzed a cohort of critically ill patients requiring MV for severe CAP in a multicenter study and found that treatment with macrolides in combination therapy according with 2007 IDSA/ATS guidelines improves survival compared to fluoroquinolones [15]. Interestingly, this protective effect of macrolide therapy was more pronounced in the more severe patients. Thus, combination therapy and especially combination therapy including macrolides seem recommended in patients with CAP caused by bacteria. The rationale for combining antibiotics in patients with CAP is based on their different mechanisms of action, resulting in synergistic killing and a broader antimicrobial spectrum; however, macrolides are linked to an anti-inflammatory effects more than anti-infective properties [33–35]. Although there is a strong body of evidence for considering combinations including a macrolide in patients with bacterial CAP, evidence for this approach in patients with viral pneumonia without bacterial co-infection is lacking. The Spanish Society of Intensive Care Medicine currently recommends patients admitted to an ICU with pandemic (H1N1)v influenza A infection should be administered combination antibiotic therapy including a third generation cephalosporin and either a macrolide or a fluoroquinolone. This recommendation is based on the current guidelines for CAP management from the Spanish Thoracic Society (SEPAR), Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC), and Spanish Society of Intensive Care Medicine (SEMICYUC) [18]. Antibiotic therapy in patients with primary viral pneumonia had to be maintained until cultures rule out bacterial infection; however, the final decision should be individualized to reduce resistance and complications related to antibiotic overuse.

Whether pandemic (H1N1)v influenza A infection proves fatal depends on the degree to which the influenza virus depresses local and general pulmonary defense mechanisms. The most common pulmonary presentation of patients affected by pandemic (H1N1)v influenza A infection is a rapidly progressive viral pneumonia with bilateral alveolar infiltrates on chest radiographs and ARDS. The presentation of ARDS with severe refractory hypoxemia has been particularly common in patients with this disease and might be linked to an abnormal immune response [36]. Investigating this hypothesis, To et al. [37] demonstrated that, due to excessive cytokine activation, patients with ARDS and those who died had slower control of viral load than patients with mild disease.

Several studies have shown promising results with the use of macrolides in viral infections. Macrolides have

Fig. 1 Propensity score distributions for patients who received macrolide-based regimens and those who did not within each propensity score quintile
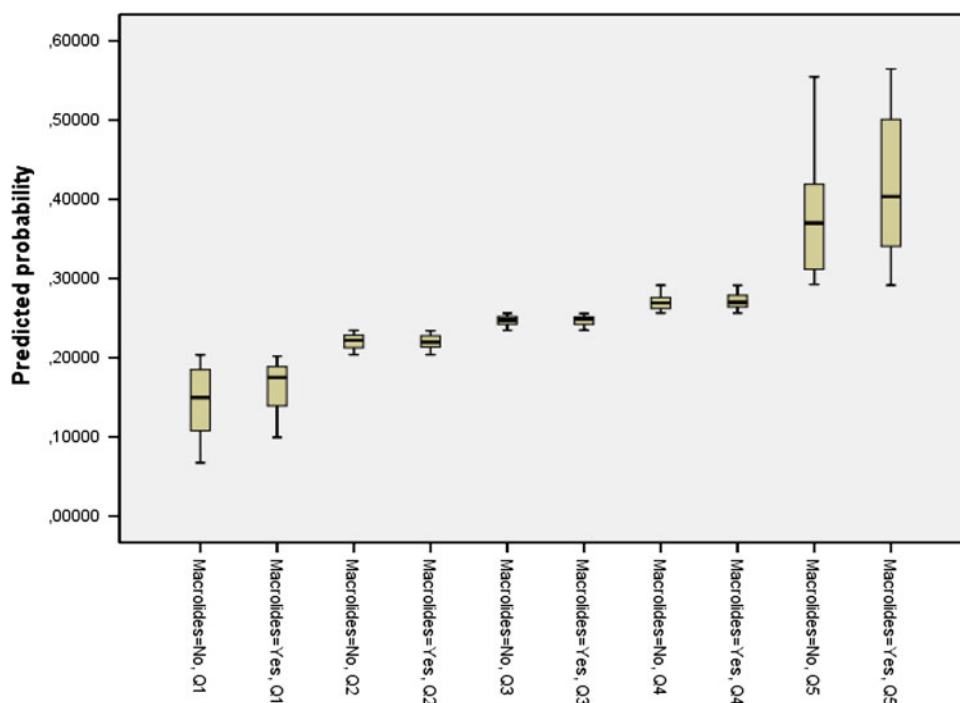
remarkable anti-inflammatory properties that exceed their antibacterial activity [33]. Animal models of H2N2 influenza virus have shown that macrolides bring about beneficial effects by decreasing interferon gamma (IFNg) and reducing the level of nitrite/nitrate (metabolites of nitric oxide) [38]. In addition, a double-blind randomized placebo-controlled trial in the treatment of respiratory syncytial virus bronchiolitis found that treatment with clarithromycin was associated with significant reductions in the length of hospital stay, the duration of need for supplemental oxygen, and the need for beta2-agonist treatment [39]. However, scant information about the impact of macrolides on the outcome of patients with H1N1 is available [40]. To our knowledge, the only study to consider the role of macrolides was reported by Viasus et al. [41]. These authors analyzed a cohort of 197 patients with pandemic influenza A (H1N1) 2009 complicated by pneumonia, only 31 of whom were treated with macrolides. They found immunomodulatory therapies (corticosteroids, macrolides, and statins) as a group were not associated with a lower risk for developing severe disease, defined as ICU admission or death; however, the overall mortality was low ($n = 3.5$ %).

The present study has several potential limitations. First, given the epidemiological nature of this study, no data about the number of patients in whom respiratory samples were obtained before antibiotic administration or the number of patients that received antibiotics before ICU admission, and this is important because the causative agent of CAP remains unidentified in 30–50 % of cases (18). In addition, because, we included all patients with negative bacterial respiratory or blood cultures, one-third of whom were not receiving mechanical ventilation, the analysis was also restricted to the subgroup of ventilated patients and similar results were obtained. Furthermore, this was an observational, non-interventional study rather than a randomized, double-blind, controlled trial in which interventions could be tightly managed and the control and treatment groups matched. However, the epidemiological characteristics and emergency nature of this disease preclude clinical trials, so we did a propensity score analysis, which replicates some of the characteristics of a randomized controlled trial, to verify and validate our results. Second, the ICUs from 148 hospitals that participated in this observational, non-interventional study were self-selected, and the decision to prescribe macrolides was made in accordance with local protocols. Although our study includes more than 70 % of all patients admitted to ICUs in Spain during the present pandemic influenza A (H1N1) virus infection [13], the present analysis enrolled patients prospectively and represents a homogeneous population from critical care settings. Likewise, we had no data on viral load secreted by the respiratory tract in our cohort of patients; however, early administration of neuraminidase inhibitors has proven a protective factor in severe cases of 2009 pandemic influenza, and the results of our study reinforce the importance of therapeutic strategies based on the early administration of antiviral drugs to control viral replication.

Our results suggest that macrolide-based treatment do not confer a survival benefit in critically ill H1N1 patients with primary viral pneumonia. One possible explanation for the lack of survival benefit is that once the exacerbated inflammatory reaction reaches a certain point, it is too late for the immunomodulatory effects of macrolides to influence the course of the disease. The potential benefit of early administration of macrolides in these patients before the instauration of respiratory failure remains to be elucidated.

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References

1. Pérez-Padilla R, de la Rosa-Zamboni D, Ponce de León S et al (2009) Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 361:680–689
2. Louie JK, Acosta M, Winter K et al (2009) Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA 302:1896–1902
3. The ANZIC Influenza Investigators (2009) Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 361:1925–1934
4. Kumar A, Zarychanski R, Pinto R et al (2009) Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA 302:1872–1879
5. WHO (2010) Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N Engl J Med 362:1708–1719
6. Rello J, Rodríguez A, Ibañez P, Socias L, Cebrian J, Marques A, Guerrero J, Ruiz-Santana S, Marquez E, Del Nogal-Saez F, Alvarez-Lerma F, Martínez S, Ferrer M, Avellanas M, Granada R, Maraví-Poma E, Albert P, Sierra R, Vidaur L, Ortiz P, Prieto del Portillo I, Galván B, León-Gil C, H1N1 SEMICYUC Working Group (2009) Intensive care adult patients with severe respiratory failure caused by influenza A (H1N1)v in Spain. Crit Care 13(5):R148
7. Kumar A, Zarychanski R, Pinto R et al (2009) Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA 302:1872–1879
8. ANZIC Influenza Investigators, Webb SA, Pettilä V, Seppelt I et al (2009) Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 361(20):1925–1934
9. Martín-Loeches I, Sanchez-Corral A, Diaz E, Granada RM, Zaragoza R, Villavicencio C, Albaya A, Cerdá E, Catalán RM, Luque P, Paredes A, Navarrete I, Rello J, Rodríguez A, H1N1 SEMICYUC Working Group (2011) Community-acquired respiratory co-infection (CARC) in critically ill patients infected with pandemic 2009 influenza A(H1N1) virus infection. Chest 139:555–562
10. Díaz E, Rodríguez A, Martin-Loeches I, Lorente L, del Mar Martín M, Pozo JC, Montejo JC, Estella A, Arenzana A, Rello J, H1N1 SEMICYUC Working Group (2011) Impact of obesity in patients infected with new influenza A (H1N1)v. Chest 139:382–386
11. Martin-Loeches I, Lisboa T, Rhodes A, Moreno RP, Silva E, Sprung C, Chiche JD, Barahona D, Villabon M, Balasini C, Pearse RM, Matos R, Rello J, ESICM H1N1 Registry Contributors (2011) Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)v influenza A infection. Intensive Care Med 37:272–283
12. Kim SH, Hong SB, Yun SC, Choi WI, Ahn JJ, Lee YJ, Lee HB, Lim CM, Koh Y, Korean Society of Critical Care Medicine H1N1 Collaborative (2011) Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. Am J Respir Crit Care Med 183:1207–1214
13. Rodríguez A, Díaz E, Martín-Loeches I, Sandiumenge A, Canadell L, Díaz JJ, Figueira JC, Marques A, Alvarez-Lerma F, Vallés J, Baladín B, García-López F, Suberviola B, Zaragoza R, Trefler S, Bonastre J, Blanquer J, Rello J, H1N1 SEMICYUC Working Group (2011) Impact of early oseltamivir treatment on outcome in critically ill patients with 2009 pandemic influenza A. J Antimicrob Chemother 66:1140–1149
14. Hiba V, Chowers M, Levi-Vinograd I, Rubinovitch B, Leibovici L, Paul M (2011) Benefit of early treatment with oseltamivir in hospitalized patients with documented 2009 influenza A (H1N1): retrospective cohort study. J Antimicrob Chemother 66:1150–1155
15. Martin-Loeches I, Lisboa T, Rodriguez A, Putensen C, Annane D, Garnacho-Montero J, Restrepo MI, Rello J (2010) Combination antibiotic therapy with macrolides improves survival in intubated patients with community acquired pneumonia. Intensive Care Med 36:612–620
16. Wunderink RG, Mandell L (2012) Adjunctive therapy in community-acquired pneumonia. Semin Respir Crit Care Med 33:311–318
17. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G, SCCM/ESICM/ACCP/ATS/SIS 2001 (2003) SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 31:1250–1256
18. Alfageme I, Aspa J, Bello S et al (2005) Guidelines for the diagnosis and management of community-acquired pneumonia. Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). Arch Bronconeumol 41:272–289
19. Mandell LA, Wunderink RG, Anzueto A et al (2007) Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44(suppl 2):S27–S72
20. http://www.msc.es/profesionales/saludPublica/gripeA/guias ProtocolosInf/pdf/ProtocoloGripe AenUCI.pdf. Accessed 07 August 2009
21. Woodhead MA, Arrowsmith J, Chamverlain-Webber R et al (1991) The value of routine microbial investigation in community-acquired pneumonia. Respir Med 85:313–317
22. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Acute Kidney Injury Network (2007) Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 11:R31
23. Suarez D, Faries DE, Propensity score regression and stratification (2010) In: Faries DE, Leon AC, Haro JM, Obenchain RL (eds) SAS Institute Inc Analysis of Observational Health Care Data Using SAS, Cary, NC, pp 23–50
24. Waterer GW, Somes GW, Wunderink RG (2001) Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 161:1837–1842

25. Baddour LM, Yu VL, Klugman KP, Feldman C, Ortkvist A, Rello J, Morris AJ, Luna CM, Snydman DR, Ko WC, Chedid BF, Hui DS, Andremont A, Chiou CCC, and the International Pneumococcal Study Group (2004) Combination antibiotic therapy may lower mortality in severely ill patients with Streptococcus pneumoniae bacteremia. Am J Respir Crit Care Med 170:400–404

26. Rodríguez A, Mendia A, Sirvent JM, Barcenilla F, de la Torre-Prados MV, Solé-Violán J, Rello J; CAPUCI Study Group (2007) Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. Crit Care Med 35:1493–1498

27. Brown RB, Iannini P, Gross P, Kunkel M (2003) Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. Chest 123:1503–1511

28. Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine MJ (1999) Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. Arch Intern Med 159:2562–2572

29. Metersky ML, Ma A, Houck PM, Bratzler DW (2007) Antibiotics for bacteremic pneumonia: improved outcomes with macrolides but not fluoroquinolones. Chest 131:466–473

30. Mortensen EM, Restrepo MI, Anzueto A, Pugh J (2006) The impact of empiric antimicrobial therapy with a β-lactam and fluoroquinolone on mortality for patients hospitalized with severe pneumonia. Crit Care 10:R8

31. Restrepo MI, Mortensen EM, Waterer GW, Wunderink RG, Coalson JJ, Anzueto A (2009) Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. Eur Respir J 33:153–159

32. Tessmer A, Welte T, Martus P, Schnoor M, Marre R, Suttorp N (2009) Impact of intravenous β-lactam/macrolide versus β-lactam monotherapy on mortality in hospitalized patients with community-acquired pneumonia. J Antimicrob Chemother 63:1025–1033

33. Tamaoki J, Kadota J, Takizawa H (2004) Clinical implications of the immunomodulatory effects of macrolides. Am J Med 117(suppl 9A):5S–11S

34. Healy DP (2007) Macrolide immunomodulation of chronic respiratory diseases. Curr Infect Dis Rep 9(1):7–13

35. Vanaudenaerde BM, Wuyts WA, Geudens N, Dupont LJ, Schoofs K, Smeets S, Van Raemdonck DE, Verleden GM (2007) Macrolides inhibit IL17-induced IL8 and 8-isoprostane release from human airway smooth muscle cells. Am J Transpl 7:76–82

36. Bermejo-Martin JF, Ortiz de Lejarazu R, Pumarola T, Rello J, Almansa R, Ramírez P, Martin-Loeches I, Varillas D, Gallegos MC, Serón C, Micheloud D, Gomez JM, Tenorio-Abreu A, Ramos MJ, Molina ML, Huidobro S, Sanchez E, Gordón M, Fernández V, Del Castillo A, Marcos MA, Villanueva B, López CJ, Rodríguez-Domínguez M, Galan JC, Cantón R, Lietor A, Rojo S, Eiros JM, Hinojosa C, Gonzalez I, Torner N, Banner D, Leon A, Cuesta P, Rowe T, Kelvin DJ (2009) Th1 and Th17 hypercytokinemia as early host response signature in severe pandemic influenza. Crit Care 13(6):R201

37. To KK, Hung IF, Li IW et al (2010) Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. Clin Infect Dis 50:850–859

38. Sato K, Suga M, Akaike T, Fujii S, Muranaka H, Doi T, Maeda H, Ando M (1998) Therapeutic effect of erythromycin on influenza virus-induced lung injury in mice. Am J Respir Crit Care Med 157:853–857

39. Tahan F, Ozcan A, Koc N (2007) Clarithromycin in the treatment of RSV bronchiolitis: a double-blind, randomised, placebo-controlled trial. Eur Respir J 29:91–97

40. Bermejo-Martin JF, Kelvin DJ, Eiros JM, Castrodeza J, Ortiz de Lejarazu R (2009) Macrolides for the treatment of severe respiratory illness caused by novel H1N1 swine influenza viral strains. J Infect Dev Ctries 30:159–161

41. Viasus D, Paño-Pardo JR, Cordero E, Campins A, López-Medrano F, Villoslada A, Fariñas MC, Moreno A, Rodríguez-Baño J, Oteo JA, Martínez-Montauti J, Torre-Cisneros J, Segura F, Carratalà J, Novel Influenza A (H1N1) Study Group, Spanish Network for Research in Infectious Diseases (2011) Effect of immunomodulatory therapies in patients with pandemic influenza A (H1N1) 2009 complicated by pneumonia. J Infect 62:193–199