Macrolides for Acute Lung Injury

In this issue of *CHEST* (see page 1153), Walkey and Wiener¹ examine the association between receipt of a macrolide antibiotic and mortality in patients with acute lung injury (ALI). The authors used existing, publicly available data from the Acute Respiratory Distress Network (ARDSNet) Lisofylline and Respiratory Management of Acute Lung Injury (LARMA) trial in which 235 patients were randomized in a two-by-two fashion to receive low tidal volume vs standard tidal volume ventilation and either lisofylline or placebo.² The exposure of interest in this study was receipt of a macrolide antibiotic within 24 h of enrollment (47 of 235 patients studied received a macrolide). After adjustment for confounding variables, patients who received a macrolide antibiotic had a significant reduction in mortality and shorter time to discontinuation of mechanical ventilation. By contrast, patients who received a fluoroquinolone or cephalosporin, compared with patients who did not, had no survival advantage, suggesting that this benefit was due to macrolides.

The antibacterial property of macrolides arises from their interaction with the bacterial ribosome and resultant inhibition of protein synthesis. However, there is growing evidence that macrolides have beneficial effects in patients with inflammatory lung diseases in addition to their ability to inhibit the replication of pathogenic bacteria. Numerous in vitro and in vivo studies have shown that macrolides mitigate inflammation and otherwise modulate the immune system. Specifically, macrolides have been shown to cause downregulation of cell surface adhesion molecules, decreased production of proinflammatory cytokines, stimulation of phagocytosis by alveolar macrophages, decreased production of reactive oxygen species, and inhibition of neutrophil activation and mobilization. In addition, macrolides reduce mucous production and bronchial hyperresponsiveness.³ The mechanism by which macrolides exert these antiinflammatory and immunomodulatory effects is not well understood.

Macrolides have proven beneficial in a number of inflammatory lung diseases, presumably because of their ability to modulate the immune response. The

addition of a macrolide to a β -lactam antibiotic was associated with higher rates of survival in patients with bacteremic pneumococcal pneumonia,⁴ and macrolides, but not fluoroquinolones or tetracyclines, were associated with improved outcomes in bacteremic pneumonia.⁵ The lack of improvement with the addition of a fluoroquinolone or tetracycline suggests that the benefit observed with macrolides is not due to an enhanced antibacterial spectrum. In a randomized controlled trial, clarithromycin improved the time to resolution of ventilator-associated pneumonia and decreased the time on mechanical ventilation but did not have an impact on mortality.⁶ Azithromycin improved lung function and reduced the frequency of exacerbations in patients with cystic fibrosis.⁷ A randomized controlled trial recently demonstrated that chronic treatment with azithromycin reduced the frequency of acute exacerbations of COPD.⁸ Treatment with macrolides slowed the progression and improved symptoms in patients with diffuse pan-bronchiolitis.⁹ Macrolide treatment of patients with asthma yielded mixed results, and there are small studies demonstrating a benefit of macrolides in the treatment of post-lung transplant bronchiolitis obliterans.¹⁰ The benefit of macrolides in these conditions, all of which are marked by inflammation, may portend a role for macrolides in the treatment of other inflammatory diseases affecting the lungs.

ALI is an inflammatory syndrome, responding to direct or indirect lung damage, that manifests clinically with the acute onset of severe hypoxemia and bilateral pulmonary infiltrates. The early, or exudative, phase of ALI is marked by diffuse neutrophilic alveolar infiltrates and accumulation of protein-rich pulmonary edema. A multitude of cytokines perpetuate the inflammation, which results in damage to the alveolar epithelium and capillary endothelium.¹¹ It is reasonable to hypothesize that the antiinflammatory and immune modulatory effects of macrolides may benefit patients with ALI. In support of this theory, treatment with macrolides leads to reduced histopathologic evidence of inflammation and lung damage as well as decreased levels of proinflammatory cytokines in animal models of lipopolysaccharide-induced ALI.¹²

The results of the current study are intriguing because they demonstrate a clear association between

receiving a macrolide antibiotic during ALI and higher rates of survival. The authors also demonstrate the utility of ARDSNet data for exploratory studies. The study is limited by its observational design and the small number of patients who received macrolides in the LARMA trial. Patients who received a macrolide were more likely to have pneumonia, less likely to have sepsis, and spent less time in the ICU and in the hospital prior to enrollment. Although the authors adjust for these differences between the groups, the potential for confounding remains. Currently, only mechanical ventilation with low tidal volumes improves survival in patients with ALI, and no known pharmacologic therapies exist. ALI is not a rare condition and carries a high rate of mortality; hence safe, effective pharmacologic treatments would be welcomed. The results of this study are promising and call for a prospective, randomized controlled clinical trial to definitively address the impact of macrolides on outcomes in patients with ALI.

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REFERENCES

1. Walkey AJ, Wiener RS. Macrolide antibiotics and survival in patients with acute lung injury. *Chest*. 2012;141(5):1153-1159.
2. The ARDS Clinical Trials Network; National Heart, Lung, and Blood Institute; National Institutes of Health. Randomized, placebo-controlled trial of lisofylline for early treatment of acute lung injury and acute respiratory distress syndrome. *Crit Care Med*. 2002;30(1):1-6.
3. Zarogoulidis P, Papanas N, Kioumis I, Chatzaki E, Maltezos E, Zarogoulidis K. Macrolides: from in vitro anti-inflammatory and immunomodulatory properties to clinical practice in respiratory diseases [published online ahead of print November 21, 2011]. *Eur J Clin Pharmacol*. doi:10.1007/s00228-011-1161-x.
4. Martínez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic reg-

imen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis*. 2003;36(4):389-395.

5. Metersky ML, Ma A, Houck PM, Bratzler DW. Antibiotics for bacteremic pneumonia: improved outcomes with macrolides but not fluoroquinolones. *Chest*. 2007;131(2):466-473.
6. Giamarellos-Bourboulis EJ, Pechère JC, Routsis C, et al. Effect of clarithromycin in patients with sepsis and ventilator-associated pneumonia. *Clin Infect Dis*. 2008;46(8):1157-1164.
7. Saiman L, Marshall BC, Mayer-Hamblett N, et al. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. *JAMA*. 2003;290(13):1749-1756.
8. Albert RK, Connett J, Bailey WC, et al; COPD Clinical Research Network. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365(8):689-698.
9. Akira M, Higashihara T, Sakatani M, Hara H. Diffuse pan-bronchitis: follow-up CT examination. *Radiology*. 189(2):559-562.
10. Friedlander AL, Albert RK. Chronic macrolide therapy in inflammatory airways diseases. *Chest*. 2010;138(5):1202-1212.
11. Wheeler AP, Bernard GR. Acute lung injury and the acute respiratory distress syndrome: a clinical review. *Lancet*. 2007;369(9572):1553-1564.
12. Tamaoki J, Tagaya E, Yamawaki I, Sakai N, Nagai A, Konno K. Effect of erythromycin on endotoxin-induced microvascular leakage in the rat trachea and lungs. *Am J Respir Crit Care Med*. 1995;151(5):1582-1588.

The Dark Side of Glycobiology in Acute Lung Injury

Despite being common and carrying an estimated mortality in excess of 30%,¹ acute lung injury (ALI) remains poorly understood. Few recent developments have improved the clinical management of affected patients. Significant advances in understanding the epidemiology and pathogenesis of ALI have been increasingly reported over the past 20 years; however, there are currently no pharmacologic interventions for the syndrome. To date, lung protective mechanical ventilation stands as the sole intervention to improve outcomes.² Only a fraction of patients exposed to predisposing environmental insults, such as sepsis or trauma, develop ALI, leading to the hypothesis that genetic variation is a significant contributor to ALI susceptibility and outcomes. Over the past decade, candidate gene approaches have suggested genetic associations related to immune system function and pulmonary permeability.³ This relatively new focus on genetic risk has the potential to elucidate novel pathways involved in the pathogenesis of ALI and contribute to personalized medicine by identifying subgroups of patients that could uniquely benefit from targeted therapy. This is particularly true as newer, larger-scale genetic approaches are applied to ALI.^{4,5} Despite these findings, the understanding of the genetics of ALI remains in its infancy relative