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Azithromycin is associated with increased survival in lung transplant recipients with bronchiolitis obliterans syndrome

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BACKGROUND: Previous studies have suggested that azithromycin improves lung function in lung transplant recipients with bronchiolitis obliterans syndrome (BOS). However, these studies did not include a non-treated BOS control cohort or perform survival analysis. This study was undertaken to estimate the effect of azithromycin treatment on survival in lung transplant recipients with BOS.

METHODS: We conducted a retrospective cohort study of consecutive lung transplant recipients who developed BOS between 1999 and 2007. An association between azithromycin treatment and death was assessed using univariate and multivariate time-dependent Cox regression analysis.

RESULTS: Of the 178 recipients who developed BOS in our study, 78 did so after 2003 and were treated with azithromycin. The azithromycin-treated and untreated cohorts had similar baseline characteristics. Univariate analysis demonstrated that azithromycin treatment was associated with a survival advantage and this beneficial treatment effect was more pronounced when treatment was initiated during BOS Stage 1. Multivariate analysis demonstrated azithromycin treatment during BOS Stage 1 (adjusted hazard ratio = 0.23, $p = 0.01$) and absolute forced expiratory volume in 1 second (FEV_1) at the time of BOS Stage 1 (adjusted hazard ratio = 0.52, $p = 0.003$) were both associated with a decreased risk of death.

CONCLUSIONS: In lung transplant recipients with BOS Stage 1, azithromycin treatment initiated before BOS Stage 2 was independently associated with a significant reduction in the risk of death. This finding supports the need for a randomized, controlled trial to confirm the impact of azithromycin on survival in lung transplant recipients.

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Lung transplantation is an important therapeutic option for patients with end-stage lung diseases. Despite its benefits, mortality rates for lung transplantation are higher than those of any other solid-organ transplantation, reaching 50% at 5 years.[1,2] Long-term survival is limited by a form of chronic allograft dysfunction known as bronchiolitis obliterative syndrome (BOS). BOS affects 40% of lung transplant recipients at 5 years and is the leading cause of death beyond the first year of transplantation.[1,2] Thus far, no therapy has clearly proven effective for decreasing mortality in BOS patients.

Azithromycin has been proposed as a potential treatment for BOS. Azithromycin is a macrolide antibiotic that has anti-inflammatory, anti-microbial and gastrointestinal promotility properties. It can inhibit interleukin (IL)-8–associated inflammation, suppress infections and prevent gastroesophageal reflux, which have all been thought to contribute to BOS.[3] Based on beneficial effects in pan-bronchiolitis

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and cystic fibrosis, azithromycin was proposed as a treatment for BOS in lung transplant recipients.[4–7] Previous studies of azithromycin for treatment of BOS have suggested improvement in lung function. These studies, however, were limited by the relatively small numbers of subjects, lacked a comparison cohort of BOS recipients who did not receive azithromycin, followed patients for only a short length of time, and contained no survival data.[7–12] We hypothesized that treatment with azithromycin would improve survival in recipients with BOS Stage 1.

Accordingly, we designed a retrospective cohort study of 297 consecutive lung transplant recipients over a 6-year period at Washington University School of Medicine/Barnes-Jewish Hospital (WUSM/BJH) to determine the effect of azithromycin therapy for BOS on survival. Subjects were censored at death or January 1, 2008, which allowed for up to 9 years of follow-up. Azithromycin-treated recipients were analyzed collectively and then separated into cohorts according to whether azithromycin was initiated prior to or after BOS Stage 2. For survival analysis, we employed univariate and multivariate time-dependent Cox regression analysis with death as the primary end-point.

Methods

Study design

Institutional review board approval for this study was obtained prior to data acquisition. A retrospective review of medical records was conducted on consecutive adult patients (age ≥18 years) at WUSM/BJH who underwent lung transplantation between August 1, 1998 and June 30, 2004. Follow-up data were accrued on all eligible recipients until death or through January 1, 2008. Demographic and clinical characteristics were obtained from medical records and computerized databases. Recipients were excluded from the study if they did not develop BOS Stage 1, could not be assessed for BOS Stage 1 (due to death within 90 days of their transplant or had insufficient pulmonary function testing due to chronic tracheostomy), or if they were treated with azithromycin long term for an indication other than BOS, such as mycobacterial disease.

Standard care of lung transplant subjects and diagnostic definitions

Pre-transplant evaluation, surgical procedures, post-operative care, surveillance bronchoscopy regimen and triple-drug immunosuppressive regimens did not change substantially throughout the study period and have been described previously.[13–16] Patients were maintained on triple-drug immunosuppression with a corticosteroid, a purine synthesis antagonist and a calcineurin inhibitor. Medication doses were adjusted according to trough levels, and immunosuppression was gradually lowered at 6 months post-operatively in the absence of recent allograft rejection. Treatment for BOS may have included azithromycin and anti-thymocyte globulin and, for continued decline in lung function, photopheresis and total lymphoid irradiation were considered. Azithromycin start date was defined as the first date that azithromycin was prescribed for BOS. The initiation of azithromycin treatment for BOS was based on a study published in 2003, and thus all patients treated with azithromycin were started subsequent to this first published report. All patients included in the azithromycin-treated cohort were started on the medication specifically for treatment of BOS without additional changes in their maintenance immunosuppression regimen.

Treatment was initiated with 5 continuous days of azithromycin at 250 mg/day, followed by 250 mg/day 3 times per week for body weight >70 kg and 500 mg/day 3 times per week for body weight >70 kg. Subjects were typically started on azithromycin for ongoing lung function decline. Therefore, azithromycin during BOS 1 was defined as azithromycin treatment that started after BOS Stage 1 but before BOS Stage 2. Azithromycin post-BOS 2 was defined as azithromycin treatment started after the onset of BOS Stage 2. Recipients in the no-azithromycin cohort predominantly developed BOS prior to 2003, and if a recipient was given only a 5-day course of azithromycin for an upper respiratory infection they were also included in the no-azithromycin cohort. Primary graft dysfunction, acute allograft rejection and BOS were diagnosed and graded using standard criteria.[17–19] The highest rejection grade (0 to 4) of acute vascular (A score) and lymphocytic bronchitis (B score) from all biopsies prior to the development of BOS Stage 1 were used as the highest A score and highest B score, respectively. Bronchoalveolar lavage (BAL) with cell counts was not done routinely during the study period. Donor organ ischemic time, cytomegalovirus (CMV) pneumonitis and community-acquired respiratory viral (CARV) infections were identified as previously defined, and pseudomonal and mycobacterial organisms were identified in respiratory specimens by standard culture techniques.[13–15]

Statistical analysis

For 2- or 3-group comparisons, we used the 2-tailed independent Student's *t*-test or analysis of variance (ANOVA), respectively, for continuous variables, and the chi-square or Fisher's exact test for categorical variables. To identify unique risk factors for death after BOS Stage 1, we used univariate and multivariate Cox proportional hazards models. A variable was included in the multivariate model if there were statistically different frequencies between the groups at baseline, if the variable was associated with death in the univariate model ($p < 0.10$), or if the variable was associated with death in previous reports. To avoid risk inflation, no more than one variable was made time-dependent in the multivariate model. For all tests, $p < 0.05$ was considered significant. The data were tabulated using Excel 2002 (Microsoft Corp., Redmond, WA) and analyzed using SPSS v13.0 (SPSS, Inc., Chicago, IL).