Azithromycin in Posttransplant Bronchiolitis Obliterans Syndrome

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To the Editor

In their excellent review of chronic macrolide therapy in inflammatory airways diseases in a recent issue of CHEST (November 2010), Friedlander and Albert[1] only briefly discuss its importance in posttransplant bronchiolitis obliterans syndrome (BOS). However, some important information is missing regarding this topic. First, we believe their review should include our retrospective cohort study, which is in fact the largest study (N = 107) with the longest duration of azithromycin treatment (mean 3.1 ± 1.9 years) in lung transplant recipients with established BOS thus far.[2] This study confirmed that long-term azithromycin improves FEV1 ≥ 10% after 3 to 6 months of treatment in 40% of patients with BOS (so-called responders), of which 33% later may nevertheless redevelop BOS, as seen in the Hannover study.[3] Responders demonstrated higher pretreatment BAL neutrophilia compared with nonresponders (median 29.3% vs 11.5%, P = .025), which decreased to a median of 4.2% (P = .041) after 3 to 6 months of azithromycin. Perhaps even more important, responders demonstrated better overall long-term survival compared with nonresponders after a mean follow-up of 6.3 ± 3.8 years posttransplantation (P = .050), a fact that was previously observed in the study by Jain et al[4] comparing with a historical BOS cohort.

Moreover, there is currently also grade A evidence that azithromycin prophylaxis actually may prevent BOS. We recently published a randomized controlled trial of patients given azithromycin, 250 mg (n = 40), or placebo (n = 43) initiated at
discharge and given thrice weekly for 2 years after lung transplantation (ClinicalTrials.gov, identifier: NCT01009619).\[5\] This study demonstrated that prophylactic azithromycin treatment not only interacts with the innate immune system, since it attenuated airway neutrophilia ($P = .015$) and systemic C-reactive protein levels ($P = .050$) over time after transplantation, but also effectively improves FEV$_1$ ($P = .028$) and BOS-free survival after transplantation (hazard ratio, 4.06; 95% CI, 1.55-7.72; $P = .0025$).

Serious adverse events were not noted in our retrospective or our prospective studies. Azithromycin, indeed, generally displays a good tolerability and is associated with a lower incidence of laboratory abnormalities, adverse events, or drug-drug interactions compared with other macrolides. In patients with subjective intolerance (mainly due to stimulation of gut motility) or rare drug interactions to oral azithromycin, aerosolized administration may perhaps represent a potential strategy to minimize adverse effects while maximizing drug delivery to the target site of disease, although this remains to be further investigated.\[6\] Another consideration in long-term low-dose azithromycin therapy is the potential selection of antibiotic-resistant organisms, for which we currently have no evidence in our center, but which may become more prevalent with increased and generalized use of azithromycin in inflammatory airways diseases.

REFERENCES: