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Evaluating Long-Term Benefits of Chronic Azithromycin

Furthering Our Quest for Precision Medicine

Interest in macrolides as a treatment for cystic fibrosis (CF) arose in the 1990s, when the effect of erythromycin on clinical outcomes in diffuse panbronchiolitis, a severe inflammatory airway disease predominantly seen in older East Asian men, was recognized (1). After initial reports of benefit (2), several randomized, placebo-controlled trials of azithromycin were conducted in adults and children with CF, with and without *Pseudomonas aeruginosa* (*PA*; Table 1).

Based on these trials, the Cystic Fibrosis Foundation (CFF) guidelines recommend chronic azithromycin (AZM) for individuals with persistent *PA* and consideration of its use for those without *PA* (3). However, antagonism between AZM and inhaled tobramycin has been observed *in vitro* and in a secondary analysis of inhaled aztreonam trials, raising concern about its safety and efficacy (4, 5).

AZM's mechanism of action in CF appears to be primarily immunomodulatory, rather than anti-infective. *In vitro*, AZM downregulates neutrophil chemotaxis and IL-8 and GM-CSF production by bronchial epithelial cells (6, 7). In clinical trials, AZM use was associated with decreased neutrophil elastase and IL-8 in *PA*-infected subjects (8) and reduced C-reactive protein, serum amyloid A, calprotectin, and absolute neutrophil count in *PA*-negative subjects (9). The only changes in microbiology noted in clinical trials were increased AZM resistance among *Staphylococcus aureus* and *Haemophilus influenzae*; no treatment-emergent pathogens were noted (10), although AZM's potential effect on the microbiome is unknown.

Although clinical trials have demonstrated short-term efficacy of AZM and led to its widespread adoption in patients with CF with chronic *PA* and, to a lesser degree, those without *PA* (11), long-term studies of the effectiveness of AZM have been lacking until now (12). In this issue of the *Journal*, Nichols and colleagues (pp. 430–437) report an analysis of the CFF Patient Registry (CFFPR) showing a significant AZM-associated reduction in FEV_1 percentage predicted (pp) decline over the course of 3 years in patients with chronic *PA* compared with those not prescribed AZM (difference, 0.88 pp; 95% confidence interval [CI], 0.30–1.47 pp) (13). Among patients without chronic *PA*, a small nonsignificant reduction in FEV_1 pp decline was found. Addressing the concern regarding AZM-tobramycin antagonism, the effect on FEV_1 pp decline in patients prescribed AZM and inhaled tobramycin was not significant, whereas those prescribed AZM and inhaled aztreonam had slower decline (0.49 pp; 95% CI, −0.11 to 1.10 pp).

The study found no benefit in reduction of exacerbations. One plausible explanation, offered by the authors, is that their analysis considered only exacerbations treated with intravenous antibiotics, whereas previous trials considered those treated with oral antibiotics as well (10). However, other explanations that address the validity of their methodologic approach are worth discussing.

Observational data from CF registries can provide insights into associations of outcomes with exposures (including therapeutics) that cannot be obtained from randomized clinical trials for ethical or pragmatic reasons. The use of these data for comparing effectiveness of therapeutics in real-world practice is attractive, but also challenging: potential methodologic pitfalls and threats to validity must be acknowledged and their consequences explicitly weighed (14). The CFFPR is an especially successful patient registry, with high-quality data on approximately 95% of the CF population in the United States and a notable history of impactful publications (15). However, studies that use any preexisting database must make pragmatic methodologic compromises to adapt and format the data set to their own needs. For example, in the current study, AZM treatment was dichotomized into low and high AZM use because CFFPR data collection does not granularly address how patients were truly prescribed AZM (3). Similar problems and solutions involved the determination of inhaled tobramycin and aztreonam use (13). Furthermore, in the real world, adherence to chronic CF therapies is about 50% (16). These challenges to appropriate classification of exposures likely bias the estimate of effect downward.

In addition, preexisting databases such as the CFFPR do not include all pertinent confounding variables relevant to a particular analysis. For studies of therapeutics, this is especially challenging because of the problem of indication bias. In clinical practice, clinicians' perception of illness severity and prognostic factors influence treatment choice. Typically, therapies are prescribed preferentially to patients deemed at high risk. This may lead to the appearance of no effect, or even an adverse effect, in population-wide analyses unadjusted for these considerations.

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Table 1. Randomized, Placebo-controlled Clinical Trials of Azithromycin

Country	Participants (*n*)	Population	*PA*-Positive	FEV_1% Predicted	Pulmonary Exacerbations (Antibiotics)	Weight
United Kingdom (21)	41	Children, adolescents	+/−	Improved	Unchanged (i.v.)	Not assessed
Australia (22)	60	Adults	All	Improved	Reduced (i.v.)	Unchanged
United States (8)	167	Children, adolescents, adults	All	Improved	Reduced (i.v. and oral ciprofloxacin)	Increased
Israel (23)	18	Children, adolescents, adults	+/−	Unchanged	Not assessed	Unchanged
France (24)	82	Children, adolescents	+/−	Unchanged	Reduced (i.v. for *PA*-positive and oral for all)	Not assessed
United States and Canada (10)	260	Children, adolescents	None	Unchanged	Reduced (oral only)	Increased

Definition of abbreviation: *PA* = *Pseudomonas aeruginosa*.

Nichols and colleagues used propensity scores, a popular approach that uses multiple patient characteristics thought to be associated with treatment and outcomes, to create suitable comparison groups (13). Although propensity matching makes optimal use of relevant CFFPR data, it cannot account for unrecorded patient characteristics known to the clinical provider that may influence the prescription of AZM. For example, tobacco exposures, mental health status, perceived adherence and disease self-management skills, and/or personal decisions to accept the prescription can be related to both treatment and outcome. However, these are not consistently recorded in the CFFPR, and thus not incorporated into the propensity scoring. These omissions can result in residual confounding and may explain, for example, why the treatment group had a more rapid rate of FEV_1 pp decline than the control group before AZM initiation (Figure 1 in Reference 13).

Additional approaches such as marginal structural modeling and inverse probability weighting can be used with propensity scoring, but remain vulnerable to bias because of unmeasured confounders (17). An alternative strategy is to focus on the potential effect of externally mediated availability or likelihood of prescribing treatment. This approach has been used in several CFFPR analyses with apparent success, using the practice patterns of individual centers as the primary unit of exposure or as an instrumental variable in two-stage least-squares analysis (18, 19). However, as discussed by Nichols and colleagues (13), the assumption that center practice fulfills methodologic criteria for an instrumental variable (i.e., consistent association with treatment and no independent association with outcome) remains unproven.

In summary, the study by Nichols and colleagues (13) effectively supports the benefits of AZM in slowing lung function decline for at least 3 years in those with chronic *PA* infection. These benefits were not observed for those prescribed concomitant inhaled tobramycin and those without chronic *PA* infections, nor in regard to exacerbations treated with intravenous antibiotics, but some concerns remain regarding residual indication bias. Furthermore, it must be considered that nonadherence to AZM may have blunted its apparent effect, which will be greater in patients who take it as prescribed. Regarding the potential antagonism between chronic AZM and tobramycin, a randomized, placebo-controlled trial is currently being conducted (NCT02677701) that promises to provide greater clarity. Given recent reports that airway inflammation is not mitigated in G551D patients treated with the CFTR modulator ivacaftor (20), the benefits of AZM in the new era of highly effective CFTR modulators will need continuing elucidation. Studies of best analytic practices for the use of data in CF registries are needed to help understand the effect of old and new therapies and provide more guidance for precision medicine for the CF population. ■

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Air Pollution and Suppression of Lung Function Growth: A Triumph for Epidemiology

The link between exposure to air pollutants such as particulate matter (PM) and nitrogen dioxide (NO_2) and suppression of growth of lung function in children and young people is now used by policy-makers to justify potentially unpopular exposure-reduction initiatives. For example, when Sadiq Kahn, the mayor of London, introduced the Ultra Low Emission Zone (ULEZ) for central London, where penalty charges are £12.50 per day for the most polluting cars and £100 per day for polluting heavier vehicles, he emphasized that "every child in London breathes toxic air daily, damaging their lung growth" (1). The current ULEZ was recognized by a C40 Cities Bloomberg Philanthropies Award in 2019, and it is proposed that, by October 2021, it will be extended to cover the area within London's North and South Circular Roads—an enlargement that will bring over 640,000 vehicles into the zone, with approximately 135,000 vehicles currently liable for the charge. A major contributor to the evidence base for lung growth suppression and air pollution is the Southern California Children's Health Study (CHS), a series of longitudinal assessments of lung function in children and young people. The seminal outputs of this study included a description of the association between background concentrations of air pollution in different communities and suppression of lung function growth (2), the independent effect of locally generated air pollution on lung function growth within communities (3), and the finding that improvement in air

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