Comparison of Inhaled Antibiotics for the Treatment of Chronic *Pseudomonas aeruginosa* Lung Infection in Patients With Cystic Fibrosis: Systematic Literature Review and Network Meta-analysis

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ABSTRACT

Purpose: In Europe, 4 inhaled antibiotics (tobramycin, colistimethate sodium, aztreonam, and levofloxacin) are currently approved for the treatment of chronic *Pseudomonas aeruginosa* lung infection in patients with cystic fibrosis (CF). Levofloxacin inhalation solution (LIS) is the most recently approved inhaled antibiotic for adult patients with CF. A systematic literature review and Bayesian network meta-analysis (NMA) was conducted to compare the relative short-term (4 weeks) and long-term (24 weeks) outcomes of these inhaled antibiotics versus LIS.

Methods: A systematic literature search was conducted on February 16, 2016, using EMBASE and Medline via OvidSP. All randomized controlled trials comparing any of the aforementioned inhaled antibiotics with 4 or 24 weeks of follow-up were evaluated. NMA was performed for the following outcomes: relative and absolute percent changes from baseline in forced expiratory volume in 1 second (FEV_1%) predicted, change in *P aeruginosa* sputum density, respiratory symptoms score from the CF questionnaire–revised, hospitalization, additional antibiotics use, and study withdrawal rates.

Results: Of the 685 articles identified, 7 unique studies were included in the 4 weeks' NMA and 9 unique studies were included in the 24 weeks' NMA. Aztreonam was predicted to result in the greatest numerically increase in FEV_1% predicted at 4 weeks, whereas LIS were predicted to be numerically greater than colistimethate sodium, tobramycin inhaled solution (TIS), and tobramycin inhaled powder (TIP). However, all of the 95% credibility intervals (CrIs) of these comparisons included zero. At 24 weeks, none of the treatments was significantly more effective than LIS. The estimates for the mean change from baseline to 24 weeks in relative FEV_1% versus LIS was –0.55 (95% CrI, –3.91 to 2.80) for TIS, –2.36 (95% CrI, –7.32 to 2.63) for aztreonam, –2.95 (95% CrI, –10.44 to 4.51) for TIP, and –9.66 (95% CrI, –15.01 to –4.33) for placebo. Compared with LIS, the odds ratio for hospitalization at 24 weeks was 1.92 (95% CrI, 1.01–3.30) for TIS, 2.25 (95% CrI, 1.01–4.34) for TIP, and 3.16 (95% CrI, 1.53–5.78) for placebo, all statistically worse than LIS. *P aeruginosa* sputum density scores, additional use of antipseudomonal antibiotics, and study withdrawal rates were comparable among all inhaled antibiotics at all times.

Implications: Based on this NMA, the analyses for many of the outcomes did not provide significant

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evidence to indicate that the other approved inhaled antibiotics were more effective than LIS for the treatment of chronic *P aeruginosa* lung infection in patients with CF. Study withdrawal rates seemed to be comparable among these inhaled antibiotics. (*Clin Ther*. 2016;38:2204–2226) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: cystic fibrosis, levofloxacin inhalation solution, network meta-analysis.

INTRODUCTION

Chronic lung infection in patients with cystic fibrosis (CF) usually involves multiple bacterial species but is frequently dominated by *Pseudomonas aeruginosa*. Chronic *P aeruginosa* lung infection is the primary cause of progressive lung function decline, increased morbidity, and mortality. Once chronic *P aeruginosa* lung infection occurs, long-term maintenance therapy with inhaled antibiotics is recommended to suppress infection, reduce acute pulmonary exacerbations, and preserve lung function.[1,2]

A variety of inhaled antibiotics in various delivery systems have been approved for the treatment of chronic *P aeruginosa* lung infection, including tobramycin, aztreonam, colistimethate sodium, and (most recently) levofloxacin. The relative efficacy of these inhaled antibiotics has not been well defined because of the lack of direct comparison among these treatments.

In 2012, Littlewood et al[3] conducted a network meta-analysis (NMA) to evaluate the relative efficacy at 4 weeks of tobramycin inhaled powder (TIP), tobramycin inhaled solution (TIS), colistimethate sodium for inhalation, and aztreonam inhalation solution for the treatment of chronic *P aeruginosa* lung infection in patients with CF. They included a total of 7 clinical trials that reported the following outcomes at 4 weeks: percent change from baseline in forced expiratory volume in 1 second (FEV_1%) predicted, *P aeruginosa* sputum density, and acute pulmonary exacerbations. The investigators reported that improvements in efficacy (as measured by changes in FEV_1% predicted at 4 weeks) were comparable between the tobramycin preparations, colistimethate sodium for inhalation, and aztreonam inhalation solution.

A systematic review of the clinical effectiveness and cost-effectiveness of colistimethate sodium for inhalation and TIP for the treatment of chronic *P aeruginosa* lung infection in CF was conducted by Tappenden et al[4] in 2013. Both colistimethate sodium for inhalation and TIP were reportedly noninferior to TIS as measured by predicted FEV_1% in the clinical effectiveness review. The investigators also assessed the viability of an NMA with key study characteristic data extracted from an additional 13 trials from 16 publications. They concluded that due to heterogeneity of the subjects' baseline characteristics among these trials and the incompleteness of the evidence network, an NMA could not be performed.

Although the 2 reviews provided some level of evidence that these inhaled antibiotics are comparable in efficacy in the short term (4 weeks), they did not include levofloxacin inhalation solution (LIS), which was recently approved in Europe, as a comparator.[3–6] It was unclear if these inhaled antibiotics have comparable efficacy profiles beyond 4 weeks. Thus, we performed a systematic literature review (SLR) and an NMA to achieve the following: (1) identify the clinical evidence for the most widely used inhaled antibiotics (tobramycin, aztreonam, and colistimethate sodium) for the management of chronic *P aeruginosa* lung infection in patients with CF; and (2) compare the short-term (4 weeks) and long-term (24 weeks) efficacy of LIS versus other inhaled antibiotics in this indication. Although safety was not assessed, study withdrawals (including withdrawals due to adverse events [AEs]) are described.

MATERIALS AND METHODS

Systematic Literature Review

The systematic literature review was undertaken according to the Centre for Reviews and Dissemination and the Preferred Reporting Items for Systematic Review and Meta-analysis.[7]

Search Strategy and Study Selection

A systematic literature search was conducted by using electronic databases EMBASE and Medline via OvidSP on February 16, 2016, to identify relevant randomized controlled trials (RCTs) of inhaled antibiotics meeting the following criteria: RCTs of patients with CF ≥6 years of age, previously treated with inhaled antibiotics, diagnosed with *P aeruginosa*