



Reducing *Pseudomonas* sputum density in bronchiectasis

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Decreased airway bacterial load may have impact on clinical outcomes in bronchiectasis. The iBEST study demonstrates that tobramycin inhalation powder reduces *P. aeruginosa* sputum density in a dose-dependent manner in patients with bronchiectasis. <https://bit.ly/3miO9fY>

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In patients with bronchiectasis, chronic infection by *Pseudomonas aeruginosa* is strongly associated with poor clinical outcomes, including more symptoms, worse quality of life, enhanced lung function decline, more frequent exacerbations and a three-fold increase in mortality [1, 2]. Therefore, treatment of chronic *P. aeruginosa* airway infection has long been regarded as a key priority in the management of bronchiectasis [3, 4]. To this end, a number of previous studies have used inhaled or nebulised antibiotics in these patients, but results are conflicting [5–9]. Most of these studies failed to reach their primary endpoints, although several potentially beneficial effects were observed. In fact, a recent meta-analysis showed that inhaled antibiotic treatment reduces exacerbation frequency in these patients [10] and, indeed, the current European Respiratory Society guidelines recommended long-term use of inhaled antibiotics in patients with chronic *P. aeruginosa* infection and frequent exacerbations [3]. Yet, many unanswered questions remain, including which is the best antibiotic agent, its dose and/or its method of administration, among others.

In this issue of the *European Respiratory Journal*, LOEBINGER *et al.* [11] report the results of the iBEST study, a phase II, randomised, double-blind, placebo-controlled study that sought to determine the efficacy and safety of different doses and forms of administration of tobramycin inhalation powder (TIP) in patients with bronchiectasis chronically infected by *P. aeruginosa*. Patients were randomised to receive three different doses of TIP (84 mg, 140 mg and 224 mg) in two different dosing regimens (continuous *versus* cyclical) [12]. Unfortunately, the study was stopped before the estimated sample size was reached. With this important limitation in mind, results indicate that all doses and administration regimens of TIP reduced the *P. aeruginosa* sputum density, and that the highest reductions were achieved in those patients who received higher antibiotic doses using a continuous administration regimen. A trend favouring TIP in terms of frequency of exacerbation episodes and use of anti-pseudomonal antibiotics was also noted, but the study had not been powered to address these outcomes. Overall, TIP was safe and well tolerated.

TIP is approved for the management of chronic *P. aeruginosa* pulmonary infection in patients with cystic fibrosis. However, evidence on TIP efficacy and safety in bronchiectasis is limited. Previous studies evaluating the effects of inhaled tobramycin in patients with bronchiectasis were done more than 10 years ago, did not use a dry powder formulation (which may have potential benefits including increased therapeutic adherence) and data on adverse events were not consistent [13–16]. Thus, the study by LOEBINGER *et al.* [11] provides new, valuable insights into the potential role of TIP in patients with

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bronchiectasis, particularly because they describe the effects of different doses and methods of administration.

The main effect of TIP in their study was the reduction of the *P. aeruginosa* density in sputum, which may have important clinical consequences. Airway bacterial load is a key component of the pathogenesis of bronchiectasis, and high airway bacterial load has been related to more airway inflammation and worse clinical outcomes [17, 18]. It is well known that inhaled antibiotics are effective in reducing bacterial load in the respiratory tract. However, its impact in clinical outcomes in patients with bronchiectasis is still unclear. A meta-analysis of 16 trials of inhaled antibiotics in 2597 patients concluded that bacterial load was consistently reduced by all inhaled antibiotics tested, but there was no effect on quality of life or symptoms [10]. More recently, though, *post hoc* analyses of randomised controlled trials showed that quality of life improved in patients with baseline high bacterial load [18] and respiratory symptoms improved during the on-treatment periods, losing its effect during off-treatment periods [19]. In this context, it is therefore important to highlight that the study by LOEBINGER *et al.* [11] is the first one to look at continuous *versus* intermittent treatment in bronchiectasis, as well as to compare different dosing regimens. Results showed that both regimens were effective in reducing *P. aeruginosa* sputum density, but this effect was higher in the continuous than the cyclical strategy. This would be in keeping with a recent report by CHALMERS *et al.* [19], showing that the administration of inhaled liposomal ciprofloxacin using 28 days on and 28 days off regimen improved symptoms during the on-period with a relapse in symptoms seen during the off-period, when bacterial loads increase back to baseline levels. This is well recognised in cystic fibrosis, where a second antibiotic is frequently administered during off-periods to prevent this rebound in bacterial load and consequent worsening of symptoms [20]. Taken together, these findings suggest that continuous inhaled antibiotic treatment may better to control chronic *P. aeruginosa* airway infection, and maintain its clinical benefits since continuous bacterial suppression appears required to reduce symptom burden and increase quality of life. Of note, however, continuous antibiotic administration may increase the risk of antibiotic resistance and antibiotic-related side effects. Although in the study by LOEBINGER *et al.* [11] no particular trend towards tobramycin resistance increases, or side-effects, were seen, further research is required to answer this crucial point.

Baseline bacterial load is another important point to consider in the interpretation of these results. Patients included in the iBEST study had a mean \pm SD *P. aeruginosa* sputum density of 6.4 \pm 1.8 log₁₀ colony forming units (CFU) \cdot g⁻¹, which is relatively high since a cut-off threshold of 7 log₁₀ CFU \cdot g⁻¹ has been proposed to define high bacterial load [17, 18]. Further, previous studies have shown that treatment with inhaled aztreonam improved quality of life only in those patients with a high baseline bacterial load, whereas no effect was seen in those with low or moderate baseline bacterial load [18]. This is important because it is possible that not all patients may benefit clinically from inhaled antibiotic treatment, and baseline bacterial load should be considered as a potential confounder in all antibiotics trials in bronchiectasis.

In summary, the iBEST study demonstrates that TIP consistently reduced *P. aeruginosa* sputum density in a dose-dependent manner in patients with bronchiectasis, with no safety issues, and suggests for the first time that a continuous regimen may be more effective than the intermittent one. These findings bring new information in the complex world of inhaled antibiotics in bronchiectasis, and position TIP as a new efficacious and safe option to treat *P. aeruginosa*-infected patients. However, further studies should address crucial questions not answered yet such as which is the target population, what is the real clinical impact on larger populations and what is the price to pay in terms of antimicrobial resistance.

Conflict of interest: O. Sibila has nothing to disclose.

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