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Treatment in Bronchiectasis to Facilitate Airway Clearance

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Abstract

Gentamicin has been used widely in the UK following the publication of this trial. It is recommended to administer the initial dose in a controlled setting like an outpatient department to detect bronchospasm prior to starting home treatment. Until recently there is a lack of large phase III trials of inhaled antibiotics, but two such trials have been recently reported.

Keywords: COPD; Lung function; Resource; Glucocorticoids; Cross-study interpretation; Reported outcomes

Introduction

Haworth studied nebulised colistin delivered via the I-Neb device. This trial recruited patients with chronic P.aeruginosa colonisation in the UK, Russia and Ukraine. The primary outcome was the time to next exacerbation, and the study narrowly failed to meet this end-point. In the secondary end-points, a large improvement in quality of life using the SGRQ was noted. The I-Neb device allows the monitoring of compliance and, in a pre-specified analysis based on patients that took the doses, a statistically significant difference in time to first exacerbation was seen. Aztreonam is an inhaled antibiotic licensed for treatment in cystic fibrosis. Two recent phase III trials in bronchiectasis randomised patients to aztreonam or placebo over the course of two 28-day treatment cycles. The primary outcome was the newly developed Quality of Life Bronchiectasis questionnaire, the first disease specific instrument to be developed [1]. Unfortunately, similar to the previous experience with tobramycin, intolerance was a major issue. Worsening of dyspnoea and cough were the major drivers of intolerance. The primary outcome was not reached, and secondary end-points such as exacerbations were also negative [2]. Several reasons for the failure of this treatment to translate into bronchiectasis can be speculated. First, the dose used was optimised for CF rather than bronchiectasis and future studies should consider specific dose-ranging studies in bronchiectasis. There were imbalances in the groups in AIR-BX1 in terms of the frequency of COPD and some markers of severity which may be relevant when considering respiratory tolerance. Finally, the heterogeneity of the population in terms of aetiology, microbiology and severity may have contributed. These negative trials are, however, not the end for inhaled antibiotics in bronchiectasis. Phase 3 trials of two formulations of inhaled ciprofloxacin have now commenced. A dry powder inhaled formulation has the potential to significantly reduce treatment burden. In a phase II study ciprofloxacin was associated with a significant reduction in bacterial load during a 28-day treatment period, without any significant differences in exacerbations. These trials have included patients with both P.aeruginosa and other bacteria, while most other trials have limited their indication to patients with chronic P.aeruginosa. This is the case for the dual release liposomal ciprofloxacin preparation. This agent aims to improve tolerability by liposomal encapsulation of the drug, reducing the amount of free drug in contact with the pulmonary epithelium, which may have contributed to previous intolerance of aminoglycosides. Slow release of the drug from liposomes allows for once-daily dosing which may also aid compliance. The phase II study showed excellent results with a significant reduction in P.aeruginosa CFU·mL−1 in the treatment arm over few weeks. There was also a reduction in time to next exacerbation.

Discussion

In contrast to the previous experience with aminoglycosides and aztreonam, however, both the dry powder and liposomal ciprofloxacin preparations were well tolerated. The current evidence for inhaled antibiotics in bronchiectasis is summarised. Therefore, the trials to date illustrate some of the issues with inhaled antibiotics in bronchiectasis. While effective in suppressing airway bacterial load, some antibiotic agents appear to have important problems with tolerability. The treatment burden associated with nebulised therapies, which include both the time to administer the dose and also to care for the machinery, are substantial and impact on compliance [3]. Mc Cullogh assessed compliance in patients with bronchiectasis and found self-reported adherence for inhaled antibiotics and for airway clearance. Patients treated with inhaled antibiotics should be assessed for adherence, medication-related adverse effects and development of resistant organisms. Although there is no evidence to support eradication per se, all of the prognostic studies to date have clearly identified P.aeruginosa persistence as an independent mortality predictor in addition to being associated with more extensive lung disease and worse pulmonary function. In keeping with recommendations in cystic fibrosis, most specialist bronchiectasis centres will attempt eradication of P.aeruginosa upon first isolation. Retrospective studies reporting high rates of P.aeruginosa eradication with treatment must be interpreted in light of data that suggests spontaneous clearance of P.aeruginosa occurs frequently in bronchiectasis both in clinical practice and in the placebo arms of randomized controlled trials. Therefore the authors will typically perform a second sputum sample pre-treatment before commencing eradication [4]. The BTS guideline provides a useful algorithm for P.aeruginosa eradication. The appropriate length of treatment for exacerbations is not known, but consensus guidelines recommend few weeks of treatment with antibiotic therapy guided by previous sputum microbiology. The only real published data are from an inpatient intravenous antibiotic study in which Murray demonstrated significant reductions in 24-h sputum volume and C-reactive protein,

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with improvements in quality of life, exercise capacity and clearance of bacteria after 2 weeks of treatment . Such data are not available to suggest if shorter durations are equally effective. There is a great need for prospective data on the management of bronchiectasis exacerbations. Surgery is now rarely employed in bronchiectasis, although in highly localised bronchiectasis with symptoms that cannot be controlled by maximal medical therapy, referral for lobectomy or segmentectomy may be considered. There are limited long-term outcome data for bronchiectasis patients after surgery and one of the largest series described an operative complication rate of 8.9% for thoracoscopic lobectomy or segmentectomy for bronchiectasis. Patients with bronchiectasis are frequently elderly, and it is important to manage associated cardiovascular disease and other co-morbidities. Anxiety and depression are very common in bronchiectasis with a reported prevalence of anxiety and of depression. These disorders also need to be recognised and managed [5]. Bronchiectasis is a heterogeneous disease with a highly variable impact on patients. Severity ranges from patients without daily symptoms who have infrequent exacerbations, to patients requiring lung transplantation. Rate of lung function decline is highly variable and is associated with P.aeruginosa colonisation and severe exacerbations. Treatments can place a large burden on patients in terms of time, and can have serious side effects for both the patient, and for the community in terms of antibiotic resistance. Therefore, patients require treatment appropriate to their stage and severity of disease. Recently, the European bronchiectasis network described the first clinical prediction tool for hospital admissions and mortality in bronchiectasis. This study, conducted in the UK, Italy and Belgium, derived a scoring system, the bronchiectasis severity index (BSI), which can accurately identify patients at the highest risk of complications, including exacerbations and impaired quality of life [6]. The authors have created an online calculation tool accessible at www.bronchiectasisseverity.com and the scoring system. This is the only prediction tool or severity classification system for bronchiectasis that has so far undergone external validation. The predictors described were independently identified by a large Spanish study which adds to the external validity of both studies. Severity of disease and risk of complications provides a useful framework for clinical decision making around which patients require long-term treatments such as macrolides, airway adjuncts, inhaled antibiotics and other measures [7]. The authors would advocate a stepwise approach to management of bronchiectasis similar to that used in asthma and COPD. Patients with bronchiectasis should be commenced on therapy at a stage appropriate to their severity of disease which should be based on clinical judgement and may be augmented by assessment of clinical severity parameters such as the BSI, exacerbation frequency or the presence of P.aeruginosa. Patients who continue to have persistent symptoms or exacerbations despite treatment at stage 1 should have their therapy escalated and so on [8]. This represents a pragmatic approach to treatment decisions that reflects how the majority of physicians practice. The difficulties of treating bronchiectasis, with a limited number of options, current therapies that are labour intensive and are associated with adverse effects. In addition, neutron-philic inflammation, which is central to the pathogenesis of bronchiectasis, has been largely resistant to existing treatments. An absence of large randomised trials has meant that there are no licensed therapies for bronchiectasis in Europe or FDA-approved therapies in the USA [9]. Much of the development of novel agents centres around targeting neutron-philic inflammation. Given the previously noted importance of neutrophil elastase in pathogenesis, this represents a promising therapeutic target. Phase II studies of oral neutrophil elastase inhibitors have been reported while others are on-going. Data show the ability to inhibit elastase activity but without clear clinical benefits yet. CXCR2 is expressed on a number of leukocytes but most prominently on neutrophils [10]. It is a key neutrophil trafficking receptor during inflammation. It also has diverse effects on inflammation as CXCR2 blockage inhibits mucus secretion both by inhibiting neutrophil recruitment and through direct inhibition of goblet cells.

Conclusion

CXCR2 antagonism is likely to reduce rather than prevent neutrophil recruitment to the airway as other chemo-attractants, particularly leukotriene B4 have been shown to be elevated in bronchiectasis and to drive neutrophil recruitment. Interestingly, the study reported higher airway inflammation despite reduced neutrophils and an increase in discontinuation due to infections.

Acknowledgement

None

Conflict of Interest

None

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