Respiratory Medicine xxx (2016) 1–8

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

The generalizability of bronchiectasis randomized controlled trials: A multicentre cohort study

James D. Chalmers [a, *], Melissa J. McDonnell [b], Robert Rutherford [b], John Davidson [c], Simon Finch [a], Megan Crichton [a], Lieven Dupont [d], Adam T. Hill [e], Thomas C. Fardon [a], Anthony De Soyza [c], Stefano Aliberti [f], Pieter Goeminne [d, g]

[a] Scottish Centre for Respiratory Research, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK
[b] Department of Respiratory Medicine, Galway University Hospitals, Newcastle Road, Galway, Ireland
[c] Institute of Cellular Medicine, Newcastle University and Adult Bronchiectasis Service Freeman Hospital Newcastle upon Tyne NE7 7DN, UK
[d] University Hospital Gasthuisberg, Respiratory Medicine, Herestraat 49, B-3000 Leuven, Belgium
[e] Department of Respiratory Medicine, Royal Infirmary of Edinburgh and the University of Edinburgh, 51 Little France Crescent, Old Dalkeith Road, Edinburgh, EH16 4SA, UK
[f] Department of Health Science, University of Milan Bicocca, Clinica Pneumologica, AO San Gerardo, Via Pergolesi 33, Monza, Italy
[g] Department of Respiratory Medicine, AZ Nikolaas, Sint-Niklaas, Belgium

ARTICLE INFO

Article history:
Received 13 September 2015
Received in revised form
19 January 2016
Accepted 22 January 2016
Available online xxx

Keywords:
Bronchiectasis
Clinical trials
Evidence-based medicine
Antibiotics

ABSTRACT

Introduction: Randomized controlled trials (RCTs) for bronchiectasis have experienced difficulties with recruitment and in reaching their efficacy end-points. To estimate the generalizability of such studies we applied the eligibility criteria for major RCTs in bronchiectasis to 6 representative observational European Bronchiectasis cohorts.

Methods: Inclusion and exclusion criteria from 10 major RCTs were applied in each cohort. Demographics and outcomes were compared between patients eligible and ineligible for RCTs.

Results: 1672 patients were included. On average 33.0% were eligible for macrolide trials, 15.0% were eligible for inhaled antibiotic trials, 15.9% for the DNAse study and 47.7% were eligible for a study of dry powder mannitol. Within these groups, some trials were highly selective with only 1–9% of patients eligible. Eligible patients were generally more severe with higher mortality during follow-up (mean 17.2 vs 9.0% for macrolide studies, 19.2%% vs 10.7% for inhaled antibiotic studies), and a higher frequency of exacerbations than ineligible patients. As up to 93% of patients were ineligible for studies, however, numerically more deaths and exacerbations occurred in ineligible patient across studies (mean 56% of deaths occurred in ineligible patients across all studies).

Conclusion: Our data suggest that patients enrolled in RCT's in bronchiectasis are only partially representative of patients in clinical practice. The majority of mortality and morbidity in bronchiectasis occurs in patients ineligible for many current trials.

1. Introduction

After decades of extrapolation of data from cystic fibrosis and COPD, recent years have seen an increasing number of randomized controlled trials for bronchiectasis [1,2]. These have provided an emerging evidence base for positioning potential new therapies and include phase 3 trials of inhaled antibiotics, mucoactive therapies and macrolides [3–8].

Unfortunately trials have struggled to recruit adequate numbers of eligible subjects and required extension to recruitment timelines and/or inclusion of new sites both of which may affect the primary outcomes [3–8]. Several of these trials have subsequently failed to meet their primary end-point [4,5,8]. To date there are no specifically licenced therapies for bronchiectasis that are supported by large scale trials.

Well designed randomised controlled trials (RCT's) and meta-analyses of trials are the highest level of available evidence. These generally form the basis of recommendations within bronchiectasis clinical guidelines [9]. RCT's often have strict inclusion and

* Corresponding author.
E-mail address: jchalmers@dundee.ac.uk (J.D. Chalmers).

http://dx.doi.org/10.1016/j.rmed.2016.01.016
0954-6111/

exclusion criteria required to limit the risk of adverse effects and to increase the likelihood of obtaining a positive outcome by controlling potential confounders. The result of this, in respiratory diseases such as COPD and asthma and in other conditions, has been that populations of patients enrolled into clinical trials are often not representative of the general population [10–12]. For example, Herland estimates that only 5.4% of asthma patients and 17% of COPD patients in Scandinavia were eligible for typical RCT's [12].

Bronchiectasis patients have significant heterogeneity in both aetiology and clinical outcomes [13–15]. Furthermore the pathophysiology of the disease is poorly understood [16]. As a result there is a risk that if RCT's are poorly representative of bronchiectasis patients, we may recommend or discard therapies based on evidence from small subpopulations. The generalizability of bronchiectasis clinical trials is therefore a key component of evaluating new evidence.

This study pooled a large, representative cohort of secondary care patients from 5 different European healthcare systems to estimate the eligibility for participation in major randomized trials of antibiotic and mucoactive therapies in bronchiectasis.

2. Methods

This analysis used combined data from observational cohort studies conducted in specialist centres in Scotland (Edinburgh and Dundee), England (Newcastle), Belgium (Leuven), Italy (Monza) and Ireland (Galway). Details of some of these cohort have been previously published and are summarised below [13,14,17,18]. All studies were approved by local ethical committees or received waivers in their respective countries. As England, Scotland and Ireland have separate healthcare systems, these 6 cohorts represent data from 5 differently constituted healthcare systems.

Although these were independent cohorts, all adhered to the British Thoracic Society guidelines algorithm for investigating bronchiectasis aetiology [9]. All clinical and spirometric data were collected while patients were clinically stable (no antibiotic use in the preceding 4 weeks). Spirometry in each institution is performed according to standard guidelines and % predicted calculated using reference values from the European Coal and Steel Community (ECSC) [19]. Diagnosis of bronchiectasis at each centre was based on the presence of radiological bronchiectasis and a compatible clinical history of cough, sputum production and/or recurrent respiratory tract infections.

Radiological severity were scored in each cohort used the modified Reiff criteria which assesses the number of lobes involved (with the lingula considered to be a separate lobe) and the severity of dilatation (tubular-1, varicose-2 and cystic-3). The maximum score is 18 and minimum score is 1 [20]. Definitions of chronic colonisation were applied as the isolation of potentially pathogenic bacteria in sputum culture on 2 or more occasions, at least 3 months apart in a 1 year period [13]. Definitions for exacerbations and requirement for intravenous antibiotics or hospital admission were at the discretion of clinicians in the individual centres, but based on the British Thoracic Society guideline recommendations [9].

The Bronchiectasis Severity Index was calculated as previous described [13].

The 6 cohort studies were largely non-selective with the exception of the Edinburgh study which excluded patients with COPD associated bronchiectasis, active non tuberculous mycobacterium (NTM), patients with HIV and patients with traction bronchiectasis secondary to interstitial lung disease [13]. The Edinburgh cohort also excluded patients taking long term oral or inhaled antibiotic therapy-details of inclusion and exclusion are shown in Table 1. This was considered to be a potential source of confounding in our current analysis but would tend to overestimate the proportion of remaining patients eligible for trial inclusion.

2.1. Inclusion and exclusion criteria of key clinical trials

Key clinical trials were identified up to September 2014 identified by the following search terms in Pubmed: Bronchiectasis AND (randomized OR placebo OR trial(s). As the objective was to identify trials of pharmacological agents approaching implementation into clinical practice, the inclusion criteria were: Published phase III trials performed exclusively in patients with non-cystic fibrosis bronchiectasis, or phase II studies for which phase III trials were actively enrolling or due to enrol in the next 12–18 months according to a search of clinicaltrials.gov and ISRCTN (http://www.isrctn.com/). Studies were excluded if they were considered to be proof of principle studies or were conducted on exacerbating rather than stable patients. Three macrolide trials were included on the basis that these drugs are widely used in clinical practice [21–24]. Studies of non-pharmacological interventions were not included.

Inclusion and exclusion criteria were extracted from source publications, online supplementary material, clinical trials protocols (where available) and study information published on clinical trials registries.

Inclusion and exclusion criteria were then applied to the original study databases on a patient by patient basis. The reason for eligibility or ineligibility were recorded. Where there was uncertainty regarding eligibility or data for a criterion were missing, the patient was assumed to be eligible. This was applied in all cases, to firstly gauge which patients could be actively screened for such trials. Secondly we applied this to avoid biasing the study in favour of our hypothesis that large numbers of patients would be found to be ineligible.

2.2. Outcomes

Follow-up outcomes over an average of 4 years follow-up were mortality, unscheduled hospital admissions for exacerbations and health related quality of life using the St. Georges respiratory questionnaire which to date is the most widely used quality of life instrument in bronchiectasis studies [25]. Exacerbations were reported for the 12 months after the baseline visit in each cohort.

2.3. Statistical analysis

Statistical analyses were performed using SPSS version 21 (IBM) and Graphpad Prism version 6. Descriptive statistics of demographic and clinical variables are presented as mean with standard deviation (SD) or median with interquartile range (IQR) dependent on distribution. Medians were compared using the Mann–Whitney U test for pairwise comparisons whilst we used the t test to compare means. Categorical data were compared with the Chi square test or the Fishers exact test where any cell contains <10 cases. For all analyses a p value < 0.05 was considered statistically significant.

3. Results

Overall 1672 patients were included in the analysis. Characteristics of the cohorts included in the study are shown in Table 1. Although conducted in different countries the cohorts had similar age ranges, with a female predominance and broadly similar rates of chronic *Pseudomonas aeruginosa* infection from 8 to 19%. The BSI scores were highly similar across the 6 cohorts indicating moderate to severe bronchiectasis with means of each cohort ranging from

Please cite this article in press as: J.D. Chalmers, et al., The generalizability of bronchiectasis randomized controlled trials: A multicentre cohort study, Respiratory Medicine (2016), http://dx.doi.org/10.1016/j.rmed.2016.01.016