RESPIRE: breathing new life into bronchiectasis

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RESPIRE, definable as "the recovery of hope, courage and strength after a time of difficulty", is apt in the context of bronchiectasis therapy. Despite its recent renaissance, including the publication of the first international guidelines for the management of bronchiectasis, only a single treatment recommendation in the 2017 European Respiratory Society guidelines was supported by high-quality evidence [1]. This is a timely reminder of the real and challenging battle ahead, to deliver evidence-based appropriate and effective therapies to patients. In this issue of the *European Respiratory Journal*, a major "blow" in this battle has been struck and appears to have landed its intended target [2, 3]. The RESPIRE 1 and 2 trials evaluated 32.5 mg ciprofloxacin dry powder inhalation (DPI) administered twice daily *versus* placebo in two separate 2×2 arm trials. Taken together, these two trials represent the largest clinical trial programme ever conducted in bronchiectasis. Each trial studied a 14- and 28-day on/off drug regime over a 48-week period. The two trials differed by: 1) their enrolling countries; and 2) statistical handling of the data. RESPIRE 1 largely enrolled across Europe, North and South America, Australia and included Japan, while RESPIRE 2 focused on Asia and Eastern Europe. The inclusion criteria were the same for each set of trials, requiring patients with bronchiectasis infected with one of a list of the most commonly identified pathogens, and a history of ⩾2 exacerbations in the previous year.

RESPIRE 1 assessed 416 patients and found a statistically significant prolongation of the time to first exacerbation and a reduced frequency of exacerbations in the 14- but not 28-day on/off regimen [2]. The 28-day on/off arm did, however, demonstrate a trend toward improvement. In contrast, RESPIRE 2 enrolled 521 patients but did not show any statistically significant improvement in either end-point but again the data appeared to trend toward benefit [3]. This is surprising for two main reasons. First, RESPIRE 2 recruitment was focused primarily in Asia and Eastern Europe, geographic locations of presumed more severe disease [4, 5]. Secondly, a very low exacerbation rate (~0.6 events·year^{-1} per patient) was recorded in RESPIRE 2 despite a clear attempt to enrich the studied population for exacerbators by enrolling those with chronic bacterial infection and ⩾2 exacerbations in the preceding year. Despite this, overall the drug was well tolerated in the tested population with minimal differences between active drug and placebo in the frequency of adverse events, although because the placebo was also a dry powder, the study design does not allow an inference to be made about the tolerability and side-

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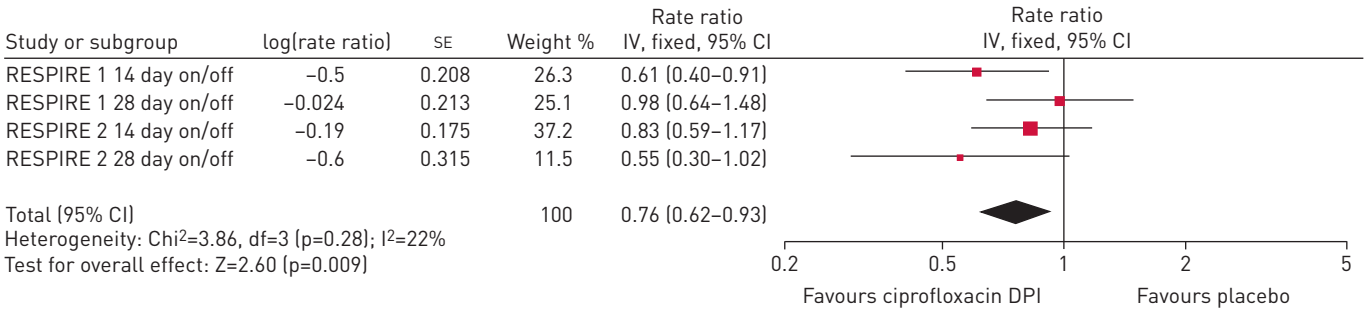

FIGURE 1 Fixed effects meta-analysis pooling of the four RESPIRE study arms for the European Medicines Agency primary outcome of frequency of exacerbations *versus* matching placebo. DPI: dry powder inhalation. Additional integrated analyses performed by the US Food and Drug Administration are available from www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiInfectiveDrugsAdvisoryCommittee/UCM584646.pdf

effect profile of dry powders in bronchiectasis. Resistance is a concern with all antibiotics and increases in minimum inhibitory concentrations to ciprofloxacin were observed.

However, the real question posed when evaluating the conclusions from both trials is "does the drug actually work?" Frequency of exacerbations is the most clinically meaningful end-point in evaluating a long-term treatment that aims to reduce exacerbations [6]. When a meta-analysis for frequency of exacerbation results are pooled from both the 14- and 28-day arms, a reasonable approach as the studies illustrate minimal difference in drug effectiveness between them, the data looks promising and heterogeneity modest (figure 1).

An average 24% reduction in exacerbations may be clinically meaningful in some patients, particularly with very frequent or debilitating exacerbations. In contrast, for patients experiencing very infrequent exacerbations, such as some subjects enrolled particularly in RESPIRE 2, the benefits may not be clinically meaningful. Therefore, a proposed answer to the posed question is yes, the drug works, and is most likely to be of benefit in selected patients with poorly controlled disease and very frequent exacerbations (*e.g.* >3 events·year^{-1}). Nevertheless, the inconsistent results between the trials make the magnitude of effect uncertain. What caused this apparent inconsistency? Why such different results in different populations? Was there anything that could have been done to improve study design?

The failure of replicate trials to reproduce results is not a new challenge for bronchiectasis. A separate body of work trialling a liposomal ciprofloxacin formulation in patients with chronic *Pseudomonas aeruginosa* infection and ⩾2 exacerbations per year has only been partially reported but encountered similar challenges to RESPIRE [7]. Published abstracts illustrate that liposomal ciprofloxacin achieved its primary end-point (time to the first exacerbation) in a single randomised controlled trial (ORBIT 4) (HR 0.72, 95% CI 0.53–0.97; p=0.03). However, the replicate ORBIT 3 trial failed to achieve the same primary end-point (HR 0.99, 95%CI 0.71–1.38; p=0.97). For the more clinically meaningful end-point of frequency of exacerbations, the corresponding data were a RR of 0.63 (95% CI 0.48–0.82, p=0.0006) for ORBIT 4 and RR 0.85 (95% CI 0.65–1.12, p=0.26) for ORBIT 3. The pooled results showed a 27% reduction in the frequency of exacerbations RR 0.73 (95% CI 0.60–0.88, p=0.0011).

The RESPIRE trials did also have limitations including cultural differences in clinical practice that potentially influenced patient selection and their subsequent inclusion, a lack of central radiological evaluation, incomplete characterisation of disease severity, higher rates of concomitant chronic obstructive pulmonary disease in RESPIRE 2 and smaller placebo *versus* treatment arms overall because of the 2:1 randomisation design. The 2:1 randomisation, while maximising the numbers of patients exposed to the study drug, does make trials such as RESPIRE susceptible to modest differences in the behaviour of placebo groups because of the relatively smaller number of subjects. With the vast heterogeneity inherent in clinical bronchiectasis, it may be wise to learn this lesson from RESPIRE and in future trials re-consider, for bronchiectasis, the traditional 1:1 trial approach. Despite this, the RESPIRE datasets are technically amenable to sub-group analysis for the identification of responders *versus* non-responders and further qualify the extent of the drug's response in the responder group. For instance, certain patient characteristics may portend toward a better response to ciprofloxacin DPI and therefore be useful in selecting appropriate patients. Additionally, the different populations in RESPIRE 1 and 2 yielded similar trends toward benefit from ciprofloxacin DPI therapy but probably with different mechanisms at work, including anti-microbial, anti-inflammatory and/or immunomodulatory effects.

A clear challenge emerging from RESPIRE and other clinical therapeutic trials in bronchiectasis is the vast ethnic, geographic and endophenotypic heterogeneity of disease [8–11]. This makes trials in bronchiectasis challenging to perform, analyse and report accurately. RESPIRE 2 is a strong case in point. Patients from different geographic regions behaved differently to what was expected with devastating consequences for the trial. Taken together, the RESPIRE trials while promising provide a clear warning that we need better methods to stratify, classify and endophenotype bronchiectasis. To avoid making mistakes of the past, we need novel approaches to ensure we identify the right group of patients, at the right time and use the right therapeutic [12]. This is only achievable with clearer precision medicine approaches for the disease which in turn is reliant on a better mechanistic understanding of its pathology and progression. For instance, several failed clinical trials in bronchiectasis including recombinant DNAase and inhaled dry powder mannitol, both effective therapies in cystic fibrosis (CF), did not translate [13, 14]. This illustrates that while the bronchiectasis appears anatomically similar to that in CF, pathophysiological differences exist and probably extend across different aetiologies. Nevertheless, no single therapeutic approach for all patients is ever likely to succeed as an approach for bronchiectasis. In fact, with the emergence of overlap syndromes, a broader, more comprehensive and complementary approach to treatment will more likely be required [15–18].

Importantly, while singular and rather one-dimensional relationships have been established in bronchiectasis, for instance *P. aeruginosa* is associated with increased exacerbations and mortality, a more realistic view is that different factors play roles in different patients to different extents [7]. This results in marked differences in outcomes and treatment responses even within groups classified by a single feature, such as the presence of *P. aeruginosa* [19]. Future clinical trials for bronchiectasis must consider patient stratification and selection more closely including potential delineation based on airway inflammation and/or specific components of the lung microbiome [11, 20–22]. A systems biology and multi-omics approach, now more widely accessible, presents an opportunity for bronchiectasis, an opportunity to combine these measures with existing clinical, immunological, microbiological and radiological data to achieve a clearer endo-phenotype for an individual patient. This will undoubtedly assist in stratification for future clinical trials and the implementation of new therapies for this orphan disease. What is, however, most difficult to address is the range of geographic and ethnic differences observed, a clear feature of RESPIRE 2. Asians, Europeans, Americans and indigenous populations all have different extents, aetiologies and severities of bronchiectasis, features that can no longer be ignored in view of the results from RESPIRE 2 [23–26]. Most publications to date have focused on large cohorts of bronchiectasis patients originating from Western Europe and the USA and, clearly more data is now required from Asia and Eastern Europe, a lesson well-taught by RESPIRE 2.

A majority of the US Food and Drug Administration's Antimicrobial Drugs Advisory committee recently voted against recommending ciprofloxacin DPI for the treatment of non-CF bronchiectasis for both regimes, although their recommendation on the 14-day on/off treatment appeared close and could have swung either way [27]. At the time of writing, a final decision on whether DPI ciprofloxacin will be approved by regulatory authorities in the USA or elsewhere has not been announced.

The bronchiectasis community should, however, be far from discouraged; we have faced similar and numerous challenges like this before and the recent trials establish clearly that inhaled antibiotics can be beneficial if targeted to the right patient population. The RESPIRE trials have provided hope for bronchiectasis but have importantly reminded us that we still have some way to go before we can fully realise our dream of providing effective and safe evidence-based treatments for this devastating disease.

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