Heterogeneity in non-cystic fibrosis bronchiectasis: insights from ASPEN trial participants

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ASPEN trial participant characteristics highlight the heterogeneity of non-cystic fibrosis bronchiectasis and global variations in clinical practice patterns https://bit.ly/447XeP0

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Bronchiectasis is a chronic and often progressive disease of the bronchi and bronchioles in which persistent inflammation and/or infection leads to permanent airway dilation and a characteristic chronic, productive cough [1]. Bronchiectasis is clinically distinguished between cystic fibrosis (CF) and non-cystic fibrosis bronchiectasis (NCFB), due to inherent differences in pathophysiology and treatment approach, and is typically characterised separately in clinical trials, registries and other studies. In both CF and NCFB, episodes of bronchiectasis exacerbations punctuate periods of relative stability and lead to hospitalisations, decreased quality of life, progressive lung function decline and increased mortality [2, 3]. As such, exacerbation prevention has become an appealing target for therapeutic development. While CF therapeutics now include disease-targeted modulator drugs in addition to inhaled treatment, there is yet to be a US Food and Drug Administration/European Medicines Agency approved therapy specifically indicated for NCFB [4, 5]. The available off-label treatment approaches for NCFB, including airway clearance, mucolytics, chronic macrolide therapy and inhaled antibiotics, have modest clinical benefit [6, 7].

In this issue of *ERJ Open Research*, Chalmers *et al.* [8] share the clinical trial design, baseline characteristics and practice pattern variations seen in the phase 3 ASPEN trial (ClinicalTrials.gov identifier: NCT04594369), which compared brensocatib (10 mg and 25 mg) to placebo in NCFB exacerbation reduction. Brensocatib is an oral, selective, competitive and reversible inhibitor of dipeptidyl peptidase 1 (DPP-1) that inhibits neutrophil elastase in a dose-dependent fashion [9]. Neutrophil elastase is a primary protease produced by neutrophils, which accounts for ~80% of the total protease activity in the body, and has been implicated in the inflammation and mucus hypersecretion during NCFB pulmonary exacerbations [10, 11]. Recently, phase 2 randomised trial (WILLOW) results showed brensocatib (10 mg or 25 mg) to improve time to first exacerbation compared with placebo, as well as an extrapolated decrease in overall exacerbations per person-year, without an increase in reported severe adverse events, over 24 weeks in 256 NCFB participants with ⩾2 exacerbations in the previous year [12–14]. Phase 3 randomised trial (ASPEN) enrolment completed in March 2023, with results expected to be available upon completion of study activities. If the ASPEN results are favourable, brensocatib may become the first drug specifically indicated for NCFB.

The more compelling data presented in the manuscript pertain to the baseline patient characteristics and the regional differences in practice patterns. Due to the heterogeneity of NCFB, with a number of different underlying aetiologies such as historical infections, primary ciliary dyskinesia, autoimmune conditions, immunodeficiencies and idiopathic processes, several registries have been established to help systemically characterise the disease [1, 15–19]. The 52-week ASPEN trial is the largest bronchiectasis randomised trial to date and enrolled 1682 adults with ⩾2 exacerbations per year from 35 countries across five continents [8]. Baseline participant data at enrolment presents a broad cross-sectional sample of the NCFB patient population at large. With 1:1:1 randomisation, a third of enrolled participants are assigned to placebo, providing an opportunity to prospectively catalogue the natural history of NCFB in the cohort. An important caveat to note is that patients were enrolled based on trial inclusion and exclusion criteria, as opposed to true

TABLE 1 Comparative characteristics of participants in ASPEN and major non-cystic fibrosis bronchiectasis (NCFB) registries

	ASPEN [8]	EMBARC [15]	US BRR [16]	RRN India [17]
Subjects, n	1682	16 963	1826	2195
Time period	December 2020–March 2023	January 2015–April 2022	2008–July 2014	June 2015–September 2017
Age, years	61.3±14.6	67 (57–74)	64±14	56 (41–66)
Female	1088 (64.7%)	10 335 (60.9%)	1439 (78.9%)	946 (43.1%)
Race		NR	Out of n=1709	NR
White	1235 (73.4%)		1514 (88.6%)	
Black	10 (0.6%)		34 (2.0%)	
Asian	189 (11.2%)		60 (4.3%)	
Other/unknown	248 (14.7%)		28 (1.6%)	
Never smoker	1169 (69.5%)	9096 (53.6%)	1094 (60.3% of n=1815)	1576 (71.8%)
Aetiology			NR	
Idiopathic	982 (58.4%)	6466 (38.1%)		470 (21.4%)
Prior infection	496 (29.5%)	3600 (21.2%)		491 (22.4%)
PCD	111 (6.6%)	506 (3.0%)		18 (0.1%)
Autoimmune[#]	~1%	972 (5.7%)		40 (1.8%)
Immunodeficiency	<1%	702 (4.1%)		NR
Asthma	Excluded	1165 (6.9%)		54 (2.5%)
COPD	Excluded	1367 (8.1%)		116 (5.3%)
TB	Excluded	825 (4.9%)		780 (35.5%)
Comorbidities				
Asthma	304 (18.1%)	5267 (31.0%)	515 (29% of 1783)	485 (22.1%)
COPD	249 (14.8%)	4324 (25.5%)	350 (20% of 1754)	512 (23.3%)
Cardiovascular[¶]	251 (14.9%)	5509 (32.5%)		355 (16.2%)
Exacerbations	NR	2 (1–4)	3.0±2.8 over 2 years	1.2±1.5
2 exacerbations per year	1190 (70.7%)	3053 (18.0%)	NR	NR
⩾3 exacerbations per year	492 (29.3%)	6584 (38.8%)		529 (24.1%)
BSI	7.1±3.6	7 (4–10)	NR	7 (3–10)
FEV_1^+, % pred	73.2±23.4	76.9 (56.0–96.7)	NR	61.4 (41.9–80.5)
BMI, kg·m^{-2}	25.5±5.1	24.9 (21.7–28.7)	23.2±5.7	21.5 (18.5–24.5)
***P. aeruginosa* positive**	600 (35.7%)	3047 (25.1% out of n=9226)	470 (33.4% out of n=1406)	301 (13.7%)
NTM positive	NR	NR	657 (50.0% out of n=1314)	8 (0.4%)
Treatment, n (%)				
Hypertonic saline	38 (2.3%)	1454 (8.6%)	NR	~5%
NAC/carbocisteine	110 (6.5%)	2910 (17.2%)		~15%
DNase	6 (0.4%)	75 (0.4%)		<1%
ICS	964 (57.3%)	8700 (51.3%)	696 (39% out of n=1794)	1387 (63.2%)
LABA	847 (50.4%)	8632 (50.9%)	NR	~60%
LAMA	278 (16.5%)	4707 (27.7%)		~30%
Inhaled antibiotic	97 (5.8%)	1310 (7.7%)	178 (10% out of n=1759)	79 (3.6%)
Macrolides	280 (16.6%)	2940 (17.3%)	NR	135 (6.2%)
Other oral antibiotic	59 (3.5%)	794 (4.7%)		137 (6.2%)

Data are presented as mean±SD, median (interquartile range) or n (%), unless otherwise stated. EMBARC: European Multicentre Bronchiectasis Audit and Research Collaboration; US BRR: United States Bronchiectasis Research Registry; RRN India: Respiratory Research Network of India; NR: not reported; PCD: primary ciliary dyskinesia; TB: tuberculosis; BSI: Bronchiectasis Severity Index; FEV_1: forced expiratory volume in 1 s; BMI: body mass index; NTM: nontuberculous mycobacteria; NAC: N-acetylcysteine; ICS: inhaled corticosteroid; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonists. [#]: Autoimmune category includes rheumatoid arthritis (RA), Sjögren disease, connective tissue diseases (CTD) and inflammatory bowel diseases (IBD) in ASPEN; RA, CTD and IBD in EMBARC; and RA in RRN India. [¶]: cardiovascular comorbidities include ischaemic heart disease in RRN India. [+]: FEV_1 % pred is post-bronchodilator in ASPEN, the equation for calculation of percent predicted is not specifically reported in each study.

random selection. Nevertheless, frequently scheduled assessments per the trial protocol at 0, 4, 16, 28, 40, 52 and 56 weeks provide data regularity not readily available in registry studies. Furthermore, protocol activities, including repeated laboratory assessments not consistently captured in registries, provide a rich dataset for multivariable modelling.

Differences between ASPEN participants and major registry patient characteristics are displayed in table 1. While patient demographics are largely similar, an important distinction is the aetiological or endotypic

differences between each study population. In NCFB, several endotypes may overlap across disease aetiologies, such as a possible type 2 inflammatory endotype in patients with concomitant asthma [20, 21]. Due to the exclusion criteria of primary asthma or COPD as the cause of NCFB, the ASPEN study population is inherently diluted in this population. However, asthma and COPD remain a high proportion of the study cohort comorbidities. Likewise, concomitant immunodeficiency and use of immunomodulatory drugs are ASPEN exclusions, thereby largely eliminating these categories of NCFB pathogenesis. As a result, these enrolment criteria selected for a study population enriched for idiopathic NCFB, when compared to registry populations. Independent of aetiology or endotype, there are also some phenotypic differences in NCFB populations. Chalmers *et al*. [2] described a "frequent exacerbator" phenotype, where ⩾3 annual exacerbations predict future exacerbations, hospitalisations and mortality. ASPEN inclusion requires a minimum of two exacerbations in the prior 12 months, thus enriching the study sample for a more severe NCFB phenotype in terms of exacerbation frequency.

It is in this context that the regional practice patterns reported by Chalmers *et al*. [8] should be considered. While registry studies have been regionally restricted, the ASPEN trial provides a global cross-sectional survey of NCFB patients meeting protocol inclusion criteria, providing data from locations without an active registry. With the exception of Africa and the Middle East, most regions are represented. Overall, there was an overuse of inhaled corticosteroid (ICS) (57.3% of participants) relative to the proportion of participants with comorbid asthma (18.1%), comorbid COPD (14.8%) or eosinophilia ⩾300 cells per µL (18.4%), an observation consistent with prior registry reports [15, 17]. However, regional differences range from 20.7% ICS use in Japan to 68.3% ICS use in Latin America, despite having the lowest regional rates of asthma and COPD in the Latin America region. Conversely, 75.9% of participants in Japan received chronic macrolide therapy, compared with 0% in Eastern Europe and 5.6% in Southeast Asia. Inhaled antibiotics use was low throughout the study (5.8%, range: 0–12.0%) despite high proportions of the study population with indications (29.3% with ⩾3 exacerbations; 35.7% culture positive for *Pseudomonas aeruginosa*) per current practice guidelines recommending inhaled antimicrobials as first-line exacerbation prevention [6, 7]. These trends are sadly reflected in registry data, potentially pointing to poor drug availability or affordability (*i.e.* insurance or national subsidisation) when drug labelling lacks specific indications for NCFB [15, 16, 19].

Though not the primary purpose of the ASPEN trial, these data may provide an opportunity to assess the reasons behind regional practice variations and differences in NCFB aetiologies. Subgroup analyses of trial results are planned, but such a valuable dataset lends the possibility of evaluating regional associations between patient comorbidities and treatment approaches. As a research community, we must first more precisely characterise the heterogeneity of NCFB in order to bring effective therapeutics to market. While brensocatib targets a common pathway in bronchiectasis, some treatment options may be reasonable/hopeful in subpopulations of NCFB patients despite lack of efficacy in NCFB patients overall [6, 7, 22]. Similarly, current available guidelines may not apply globally due to regional differences in patient presentations (*e.g.* tuberculosis is the most frequent aetiology for NCFB in India) [17]. Lastly, additional phenotyping such as "progressive" *versus* "non-progressive" NCFB may further improve our precision in therapeutic development and clinical care.

Despite the limited generalisability due to ASPEN's inclusion criteria selecting for a subset of NCFB populations, Chalmers *et al*. [8] present baseline characteristics which provide important details about the global make-up of the NCFB community, as well as information regarding regional practice pattern variation to help inform future studies. The wide practice pattern variation seen in this study, potentially not always in line with current best practices, suggests a need for identification of regional barriers to delivery of guidelines-directed care. However, identification of such significant regional variation may also support a more global and inclusive approach to future guidelines development to encapsulate the broad heterogeneity of global NCFB.

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