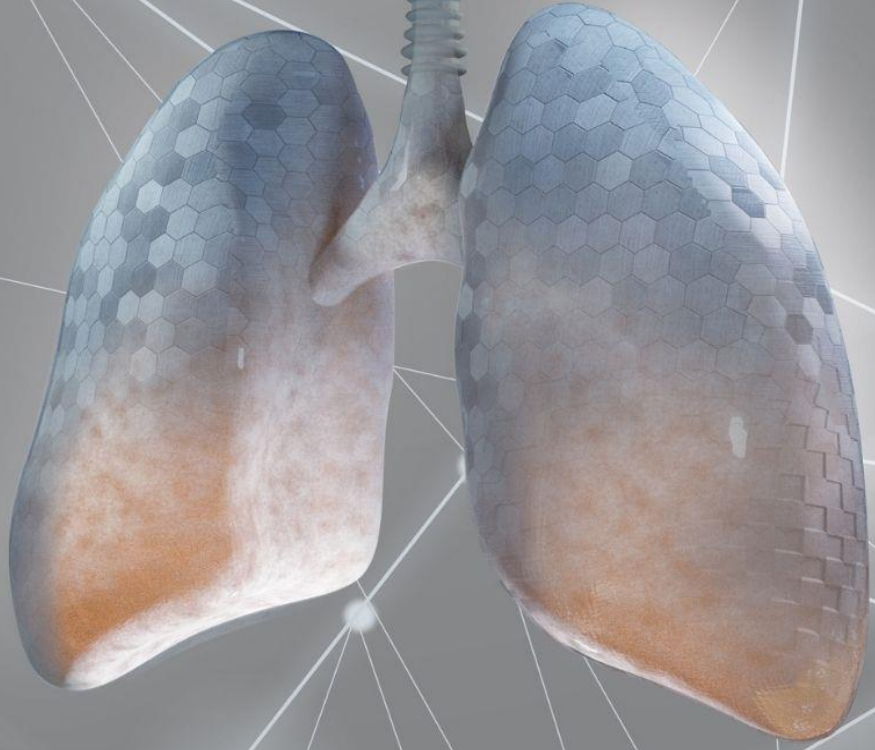
NTM
Bronchiectasis



2ND EUROPEAN NTM & BRONCHIECTASIS WORKSHOP

VIRTUAL EDITION

30TH JUNE – 3RD JULY 2021

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Computer aided analysis of airway-artery dimensions for objective diagnosis and monitoring of bronchiectasis and airway wall thickening in patients with Cystic Fibrosis.

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Background

Cystic Fibrosis (CF) lung disease is characterized by progressive diffuse airway wall thickening (AWT) and bronchiectasis (BE). Manual analysis of all visible airway-artery (AA) pairs on chest computed tomography (CT) scans of patients with CF has been shown to be a sensitive method to detect and monitor CF airways disease. However, this manual method is extremely time consuming, why we developed a fully automated AA-method.

Aim

To validate the fully automated AA method for objective and sensitive assessment of airways dimensions on CT in an external cohort of CF patients.

Methods

The ErasmusMC LungAnalysis group and Thirona jointly developed and validated the AA-LungQ (Thirona) software to fully automatically: 1) identify the airway tree and matching arteries 2) identify generation (G) for each AA-pair 3) measure for each detected AA-pair: outer airway wall diameter (A_{out}), inner airway wall diameter (A_{in}), airway wall thickness (A_{wt}) and diameter of the paired artery (A) and 4) compute the following ratios for each AA-pair: A_{out}/A; A_{in}/A; A_{wt}/A and present the ratios for each CT starting at the first segmental bronchi (G_1) up to the last visible G.

AA-lungQ was trained and tested on subsets of 40 CTs from the ErasmusMC CF cohort. For validation, 111 spirometry controlled CTs of the Copenhagen CF cohort (6 to 18 years) were previously scored using PRAGMA-CF (Sandvik, JCF 2020) and were analysed using AA-LungQ. %AWT and %BE were defined as the ratio of A_{wt}/A >0.33 and A_{out}/A >1.18 ($\%BE_{out}$) or A_{in}/A >1.04 ($\%BE_{in}$) out of all AA-pairs for each G. Regression models were used to correlate %AWT to PRAGMA-CF %AWT and $\%BE_{out}$ and $\%BE_{in}$ to PRAGMA-CF%BE.

(Sponsored by Dutch CF foundation through a PPS grant).

Results

18,041 AA-pairs were identified from generation 1 to 14 in 111 patients. Mean (SD) number of AA-pairs per patient was 163 (87.5) AA-pairs.

Adjusted R^2 of the regression models for %AWT vs PRAGMA-CF%AWT , $\%BE_{out}$ vs PRAGMA-CF%BE, and $\%BE_{in}$ vs PRAGMA-CF%BE were 0.321 (H_0: coefficient = 0, P<0.001), 0.578 (P<0.001), and 0.435 (P<0.001), respectively.

Conclusions

In the external cohort, airway wall thickening and bronchiectasis assessed automatically using AA-LungQ correlated well to PRAGMA-CF sub-scores for airway wall thickening and bronchiectasis.

Further validation work is ongoing in longitudinal CF cohorts to assess its ability in different age groups to track and monitor disease progression and its performance in non-CF lung disease, bronchiectasis, asthma, primary ciliary dyskinesia etc..

Mepolizumab in severe eosinophilic asthma patients with co-presence of bronchiectasis

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Background: The association of bronchiectasis (BE) in patients with severe eosinophilic asthma (SEA) is quite frequent. Mepolizumab is a well-recognized treatment for SEA. We evaluated its effectiveness in SEA patients with and without BE in real-life.

Methods: We performed a single-center pilot study, including patients with SEA treated with mepolizumab for one year. Bronchiectasis were diagnosed on chest-CT scan, according to the following criteria: 1) internal diameter of the bronchus greater than that of the adjacent pulmonary artery, 2) lack of tapering of the bronchial lumen toward the lobe periphery. Asthma control test (ACT), lung function, annual exacerbations rate, oral corticosteroid (OCS) intake, chronic mucous hypersecretions (CMH), blood eosinophil count and sputum eosinophils and neutrophils were recorded at baseline and after 12 months. Bronchiectasis Severity Index (BSI) was calculated.

Results: We included 32 Severe Eosinophilic Asthma (SEA) patients (mean age: 52.3±10, 59% female). Sixteen out of 32 (50%) showed co-presence of bronchiectasis (SEA+BE). We found an inverse linear relationship at baseline between BSI, ACT score (r = -0.7381, p=0.0016) and FEV1 % (r = -0.5962, p=0.0165). Significant improvements were reported in terms of ACT score [SEA from 13.8±4.6 to 21.8±3.1, p<0.001; SEA+BE from 13±4.8 to

20.7±5.5, p<0.001], annual exacerbations rate [SEA from 7 (4-12) to 0 (0.00-0.75), p<0.001; SEA+BE from 8 (4-12) to 0 (0-1), p<0.001], blood eosinophils count (p<0.001) and OCS intake [SEA from 15 mg (0-25) to 0 mg (0-0), p=0.003; SEA+BE from 8.8 mg (0-25) to 0 mg (0-0), p=0.01] after 12 months of treatment. CMH was referred by 87.5% (15/16) in the SEA+BE group, reduced to 25% (4/16) after mepolizumab (p=0.0011). Sputum eosinophil count reduced from 26.5% (10.8-62.8) to 12.5% (5-23) (p<0.0001) in SEA+BE group and from 20.5% (17.3-42.3) to 9% (7-10) at (p<0.0001) in SEA group. Furthermore, sputum neutrophils decreased from 24.5% (8.3-48.3) to 14.50% (4-29.8) (p=0.012), in SEA+BE. According to BSI, 7 (44%) patients had a low BSI and 9 (66%) a moderate-to-severe BSI. Despite the latter had baseline lower ACT score (10.3±3.5 vs. 16.4±4.2, p=0.009) and FEV1% (60.8±17.6 vs. 90.3±23.5, p=0.008) no statistically different results were obtained between the groups in every outcome, except for FEV1% [96.7±18.2% Low-BSI vs 71.3±18% moderate-to severe BSI, p=0.03] after 12 months of treatment.

Conclusions: Mepolizumab effectively improves asthma symptoms control, reducing annual exacerbations and corticosteroid intake in patients with SEA, even in the subgroup with coexisting bronchiectasis, independently of their severity. In addition, the number of SEA + BE patients reporting CMH, as well as sputum eosinophils and neutrophils, decreased. This raises the hypothesis that mepolizumab may also play a role in blocking the "Cole’s cycle" in patients with co-morbid BE.

Characteristics of bronchiectasis in Korea – first data from the KMBARC registry and comparison with other international registries

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Background: Understanding the aetiology and characteristics of patients with bronchiectasis is vital for developing strategies to reduce the burden of disease; however, geographical variations in these characteristics make it difficult to formulate a uniform strategy for investigation. Hence, this study aimed to describe the burden of illness and treatment among Korean bronchiectasis patients and compare the results with those from three geographically and ethnically diverse regions: Australia, Europe, and India.

Methods: The Korean Multicentre Bronchiectasis Audit and Research Collaboration (KMBARC) is a prospective, non-interventional observational study. The KMBARC registry design and data collection fields are closely aligned with those used by the Australian, European, and Indian registries. Korean (n = 598; 2018–2019) and Australian (n = 653; 2016–2020) were analysed for this study, and European (n = 2,596) and Indian (n = 2,195) data were obtained from a previously published study.

Results: Most patients in all cohorts were aged > 60 years and predominantly females; however, Indian patients were nearly 10 years younger on average and predominantly males. Regarding comorbidities, Korean patients showed a lower prevalence of ischemic heart disease and a higher prevalence of chronic obstructive pulmonary disease than those in other bronchiectasis registries. The bronchiectasis severity index of Koreans (median 6) was comparable with that of Europeans (median 6) and Indians (median 7). However, the bronchiectasis severity index of Australians (median 9) was

relatively higher than that recorded in other registries. The rate of experiencing more than one hospital admission in the previous year was highest for Indians (38.8%), followed by Australians (30.5%), Europeans (25.9%), and Koreans (18.2%). Regarding pulmonary function, Australians had the highest forced expiratory volume in 1 second(%predicted) (median 79.4), followed by Europeans (median 73.8), Koreans (median 65.4), and Indians (median 61.4). *Pseudomonas aeruginosa* was the most common causative pathogen among Koreans, Australians, and Indians, whereas *Haemophilus influenzae* was the most common in Europeans. The two most common causes of bronchiectasis were idiopathic and tuberculosis (TB) in Koreans. In comparison, the two most common causes of bronchiectasis in the Australian and European registries were idiopathic and post-infective, whereas in the Indian registry, the most common causes were TB and post-infective. The rate of prescribing long-term antibiotics was highest in Australians (31.4%), followed by Europeans (19.4%), Indians (12.3%), and Koreans (3.9%).

Conclusion: There were significant differences in the aetiology, comorbidities, and treatment of bronchiectasis among the different countries and regions. We believe that the clinical guidelines for bronchiectasis in individual countries need to address these issues based on epidemiological data because they may vary from country to country.

Acknowledgement: This study is recently accepted for publication in *Respirology* and may be published online when the workshop is held.

MGIT time-to-positivity is an early biomarker of treatment response in Mycobacterium avium complex pulmonary disease

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BACKGROUND
The recommended treatment regimen for *Mycobacterium avium* complex pulmonary disease (MAC-PD) consists of 3-drugs: rifampicin (or clofazimine), ethambutol and azithromycin. Intravenous amikacin is added for severe disease. Culture conversion is the best marker for treatment response but takes up to 6 months. Hence, there is a need for an early biomarker to predict treatment response. We studied the use of time-to-positivity (TTP) of the Mycobacterium Growth Indicator Tube (MGIT) automated broth culture system as a biomarker for treatment response in MAC-PD.

METHODS

We performed a retrospective review of adult patients with macrolide-susceptible MAC-PD, who received treatment >6 months at our reference clinic in the 2013-2019 period; patients were excluded if no sputum culture was performed after 6 months of treatment, if <3 sputum cultures were performed or if no TTP data was available.

Demographic data, fibro-cavitary versus nodular-bronchiectatic manifestation, treatment regimen and culture status after 6 months of treatment were recorded. We defined culture conversion as 2 consecutive negative cultures, collected ≥4 weeks apart.

Sputa were decontaminated using NALC-NaOH, concentrated and inoculated in MGIT tubes. Isolated mycobacteria were identified using the InnoLiPA Mycobacteria v2 line probe assay. Machine-generated TTP data of MGIT liquid culture were rounded to days.

RESULTS

We included 49 patients; characteristics are in Table 1. After 6 months of therapy, 34/49 (69.4%) patients attained sputum culture conversion. Mean baseline TTP was significantly higher in converters than in non-converters (7.68±4.64 vs. 4.87±2.20 days; p=0.031); it was also significantly different between patients with nodular-bronchiectatic disease and those with fibro-cavitary disease (8.86±5.62 vs. 5.29±1.65 days; p=0.010) but disease manifestation was not significantly associated with culture conversion (p=0.371). ROC curve analysis suggests a cut-off at a TTP of ≥8 days, which predicts culture conversion with a sensitivity of 43% and specificity of 93%.

Differences in TTP increased after three months of treatment (36.38±12.30 days in converters vs 9.75±5.19 in non-converters; p<0.001). The mean absolute difference (TTP at 3 months – TTP baseline) was 28.50±11.96 in converters and 4.50±6.56 in non-converters (p=0.001).

CONCLUSIONS

MGIT TTP data obtained at baseline and in the first three months of MAC-PD treatment can be used to predict sputum culture conversion in MAC-PD treatment. This early and easily available biomarker can be a useful tool in clinical practice as well as in trials evaluating new therapies.

Table 1: Baseline characteristics of the 49 MAC-PD patients

Table 1: Baseline characteristics of the 49 MAC-PD patients

Manifestation	Fibro-cavitary (n=28)	Nodular-bronchiectatic (n=21)	Total (n=49)
Females *n* (%)	11 (39%)	16 (76%)	27 (55%)
Mean age (year)	61.3±8.8	67.8±10.1	64.0±9.9
M. avium	11	11	22
M. intracellulare	6	6	12
M. chimaera	11	4	15
Mean baseline TTP (days)	5.29±1.65	8.86±5.62	6.82±4.23
3-drug regimen	20	20	40*
4/5-drug regimen	8	1	9**
Culture conversion after 6 months n (%)	18 (64%)	16 (76%)	34 (69%)
Cure at end of treatment	12 (43%)	12 (57%)	24 (49%)

** amikacin-clofazimine-rifampicin-ethambutol-azithromycin (n=8), clofazimine-rifampicin-ethambutol-azithromycin (n=1) or or amikacin-rifampicin-ethambutol-azithromycin (n=1)

Neutrophil Serine Protease Levels in Blood and Sputum Samples of Patients on a Reversible Dipeptidyl Peptidase 1 (DPP1) Inhibitor from the WILLOW Phase 2 Trial in Non-Cystic Fibrosis Bronchiectasis

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Background: Brensocatib is an oral, selective, reversible inhibitor of dipeptidyl peptidase I (DPP1); an enzyme responsible for activating neutrophil serine proteases (NSPs) including neutrophil elastase (NE), proteinase 3 (PR3), and cathepsin G (CatG). NSPs play an essential role in pathogen destruction and inflammatory mediation. However, in chronic inflammatory lung diseases such as non-cystic fibrosis bronchiectasis (NCFBE), neutrophils accumulate in the airways resulting in excess active NSPs that cause damaging inflammation and lung destruction. In the six-month Phase 2 WILLOW trial in NCFBE, treatment with brensocatib was associated with improvements in clinical outcomes including reduction in exacerbations. As part of an exploratory analysis, the effect of brensocatib on NSP levels in blood and sputum was evaluated.

Methods: NCFBE patients were randomized to once-daily placebo (n=87), or brensocatib 10 mg (n=82) or 25 mg (n=87). NSP levels were measured in sputum and blood at baseline and at 2, 4, 12, 24 (end of treatment) and 28 weeks. Levels of active NE, PR3 and CatG in sputum were measured after dilution (200x, 50x, 10x, 1x) using a commercial immunoassay kit (ProAxsis). All readouts below the limit of quantitation (LOQ) were converted to the LOQ values. Changes in NSP sputum levels over time were assessed by calculation of geometric means. Levels of active NE and PR3 in blood were determined following lysis of white blood cell pellets and analysis of supernatants in enzymatic assays by monitoring the rate of release of a fluorophore from peptide substrates specific to NE or PR3. Changes in NSP blood levels over time were assessed by calculating arithmetic means. Statistical analyses were performed using GraphPad Prism.

Results: A dose dependent reduction in NE, PR3 and CatG was observed in sputum and for NE and PR3 in blood after four weeks of brensocatib treatment with a return to baseline at week 28. In sputum, after 4 weeks of treatment, active NE was reduced by 86% and 91% for 10 and 25 mg brensocatib treatment, respectively, to 214 and 141 ng/mL compared to placebo at 1514 ng/mL. Active PR3 was reduced by 21% and 53% for 10 and 25 mg brensocatib treatment, respectively, to 2309 and 1368 ng/mL compared to placebo at 2927 ng/mL. And active CatG was reduced by 90% and 93% for 10 and 25 mg brensocatib treatment, respectively, to 6 and 4 ng/mL compared to placebo at 56 ng/mL. In contrast, in blood, after 4 weeks of treatment, active NE and

PR3 were reduced by 61% and 41%, respectively, for 25 mg brensocatib, and by 20% for NE for 10 mg brensocatib with no reduction for PR3, compared to placebo.

Conclusions: Brensocatib produced the greatest reduction in the percentage of activity of CatG (sputum), followed by NE (sputum and blood) and then PR3 (sputum and blood). A greater reduction of NE and PR3 activity was observed in sputum than for blood, suggesting that it is not necessary to completely inhibit DPP1 to have a meaningful impact on lung markers of inflammation.

P.01 Results of a drug susceptibility study of non-tuberculous mycobacteria isolated from patients with Nontuberculous Mycobacterial Pulmonary Disease

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Over the past 5 years, the possibilities of detecting non-tuberculous mycobacteria (NTM) and determining their drug sensitivity have significantly expanded in the Republic of Belarus. The republic has a new algorithm for the species identification of NTM using molecular genetic methods. Thanks to this, the diagnosis of nontuberculous Mycobacterial Pulmonary Disease (NTM-PD) has significantly improved. To date, researchers have a clear understanding that the effectiveness of treatment of a patient with NTM-PD directly depends on the determination of the drug sensitivity (DR) of the isolated NTM.

Objective*:* to determine the drug sensitivity of clinically significant NTM to aminoglycosides and macrolides.

Subject of the study: 114 cultures of NTM isolated from patients with an established diagnosis of ML. All laboratory and instrumental studies necessary for the diagnosis and monitoring of bacterial excretion in patients with NTM-PD were performed on certified equipment that meets international quality control requirements, in the conditions of clinical and laboratory departments of the *Republican Research and Practical Centre for Pulmonology and Tuberculosis*.

Research methods. The etiological role of NTM in lung disease was established in accordance with the criteria of ATS / IDSA (2007), BTS (2017) [Haworth C. S. et al. British Thoracic Society guidelines for the management NTM-PD, 2017]. In each case, the presence of a combination of microbiological and clinical criteria for NTM-PD was established, provided that tuberculosis was excluded. Microbiological criteria included the presence of two or more positive sputum culture results with the same type of NTM isolated during the year. Microbiological criteria included the presence of two or more positive sputum culture results with the same type of NTM isolated during the year. The clinical criteria are the presence of respiratory complaints and changes according to high-resolution computed tomography. The NTM species was established by molecular genetic identification using GenoType Mycobacterium CM / AS (Hain Lifescience, Germany) and by hybridization with DNA probes (LPA). GenoType NTM-DR ver. Kits were used to determine the LS to aminoglycosides and macrolides of clinically significant NTMP 1.0 (Hain Lifescience, Germany). According to

the manufacturer's instructions, testing with the GenoType NTM-DR kit can be performed to detect resistance to macrolides and aminoglycosides in the following representatives of NTM: M.avium, M. intracellulare, M. abscessus, M.chelonae.

***Results and findings*.** Detection of clinically significant types of NTMs in patients with NTM-PD showed that the main biological environment allowing the isolation of pathogenic mycobacteria in 96.69% of cases is sputum. In isolated cases, NTM culture was isolated from pleural fluid, bronchoalveolar lavage, and lung tissue. The analyzed sample of crops contained both slow- and fast-growing NTM species. The detected slow-growing mycobacteria included representatives of the M. avium complex (MAC): M. avium (n = 81) and M. intracellulare (n = 15). A combination of M. avium + M. intracellulare was detected in 3 sputum samples from patients with NTM-PD. From fast-growing NTMBs, the following were found: M.abscessus (n = 4), M. chelonae (n = 7). As it turned out, 56 isolated cultures of NTM (49.12%) had LS immediately to 2 groups of antibacterial agents. Fifteen (13.15%) NTM cultures were sensitive only to macrolides. Sensitive cultures of NTMs only to aminoglycazides were not identified. Macrolide resistance was observed in 4 (3.51%) NTM cultures. In the studied sample in 39 NTM cultures, the results of the study on the LS were not definite.

The results of the study of DS in isolated cultures of NTMB from patients with NTM-PD showed that mycobacteria of the MAC-complex were characterized by high sensitivity to drugs of both groups. Thus, 85.18% (69 out of 81) cultures of M. avium showed sensitivity to both macrolides and aminoglycosides. In the remaining 9.87% (8 out of 81) representatives of the M.avium culture, LP was detected only for macrolides. M. intracellulare cultures in 80% of cases also had a sensitivity to antibacterial drugs of both groups.

In this study, all isolated M. abscessus cultures were sensitive to macrolides and resistant to aminoglycazides. Most M. chelonae showed sensitivity to both antibiotics - 71.42%. However, taking into account the small number of isolated cultures of these types of mycobacteria, it is premature to draw conclusions about the presence of a certain pattern.

It should be noted that the study of the DS of clinically significant NTMs is actively carried out by different countries. However, the results of these studies cannot be compared, since, firstly, the NTM cultures themselves may have genetic differences, and, secondly, the methods for diagnosing DS NTMs at this point in time are not brought to a common standard.

P.02 Familiar Alpha-1 antitrypsin deficiency (AATD) and increased risk of lung infections due to various Actinomyces.

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Background: AATD is an autosomal co-dominant genetic condition that can result in serious lung disease in adults. AATD is the prototype of the endogenous inhibitor of serine proteases such as neutrophil elastase (NE), which is responsible for direct damage to lung epithelial cells and supportive tissues. Though NE is mainly involved in the response against bacteria, it can cause several detrimental effects, including extracellular matrix destruction, mucus gland hyperplasia and increased mucus production, reduction of ciliary beating rate, and direct damage to the airway epithelium. The association between AATD and bronchiectasis is reported in several studies, but it is unclear whether AATD may increase susceptibility to specific infections.

Case Presentation: A 86- years -old woman, C.M.A, was initially diagnosed in 2010 with Non-Tuberculous Mycobacterial lung disease (NTM-LD) caused by *Mycobacterium avium*. The treatment -clarithromycin, rifabutin and ethambutol- lasted twelve months. The NTM-LD relapsed three years later and the patient was treated with the same regimen for twenty-four months. Her last Chest Computer Tomography (CT) scan showed middle lobe bronchiectasis (Fig.1A).

In late 2019, her 80 years - old sister, C.R, also resulted affected by NTM-LD due to *M. avium*. The ongoing out-patient treatment was azithromycin, rifampicin and ethambutol. CT scan was characterized by bilateral consolidation, middle lobe bronchiectasis and micronodules (Fig.1B).

In April 2020, their 83- years old brother, C.A., presented bilateral bronchiectasis and two consolidations with irregular margins in the left upper lobe at the thorax CT scan (Fig.1C). Sputum culture was positive for *Nocardia Cyriacigeorgica* and the patient was treated with Trimethoprim/ Sulfamethoxazole for six months. In June 2020 C.A was tested for AATD. The Genotyping Test resulted positive for c.863A>T heterozygous mutation (PI*MS) and serum AAT concentration was normal. Subsequently, his sisters were also tested with a positive result for the same mutation and serum concentrations.

Conclusion: This report highlights the importance of searching for AATD

during bronchiectasis screening. Recent studies show that AAT probably has antimicrobial and anti-inflammatory properties that may protect against bacterial infections in the lung. Mycobacteria and Nocardia are both part of the Actinomyces family. Chan et Al analyzed a cohort of 100 patients with NTM lung diseases, 27% of that cohort had anomalous AAT protein, but to our knowledge, there were no links reported between Nocardia infections and AATD.

Further studies are needed to evaluate the association between AATD and respiratory infections supported by opportunistic pathogens such as NTM or Nocardia.

P.03 Targeting Neutrophilic Inflammation in Bronchiectasis: Design of the Phase 3, Randomized, Double-Blind ASPEN Study Examining Efficacy and Safety of DPP-1 Inhibition

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BACKGROUND/AIMS

Neutrophil serine proteases (NSPs), including neutrophil elastase (NE), are activated by dipeptidyl peptidase-1 (DPP-1) during neutrophil maturation and are central to the pathogenesis of several chronic inflammatory diseases, including non–cystic fibrosis bronchiectasis (NCFBE). Brensocatib, an investigational, oral, selective, and reversible DPP-1 inhibitor that blocks NSP activation, is hypothesized to reduce the risk of exacerbations through inhibition of the inflammatory cascade. In the phase 2 WILLOW trial (Chalmers et al. *N Engl J Med.* 2020), brensocatib over 24 weeks prolonged time to first exacerbation, reduced frequency of exacerbation and decreased sputum NE levels compared with placebo in patients with NCFBE. The objective of the phase 3 ASPEN study (NCT04594369) is to assess the safety and efficacy of brensocatib over 52 weeks compared with placebo in patients with NCFBE.

METHODS

ASPEN is an ongoing, randomized, double-blind, placebo-controlled, multicenter study in which adults (18-85 years old) with NCFBE and ≥2

exacerbations in the past 12 months are randomized 1:1:1 to receive brensocatib 10 mg, brensocatib 25 mg, or placebo once daily for 52 weeks. Assessments occur during both in-clinic visits (baseline; weeks 4, 16, 28, 40, and 52; and end of study at week 56) and telephone visits (weeks 10, 22, 34, and 46). The primary endpoint is the frequency of exacerbations over the 52-week treatment period, comparing both brensocatib doses vs placebo. Secondary efficacy endpoints include time to first exacerbation, frequency of severe exacerbations, lung function, and quality of life. Safety endpoints include incidence and severity of treatment-emergent adverse events.

RESULTS

The ASPEN study is designed to demonstrate superiority of brensocatib treatment over placebo as measured by the primary efficacy endpoint of the frequency of exacerbations. Assuming the annualized exacerbation rate in the placebo arm is 1.2 events with a negative binomial distribution with dispersion of 1, a total of 1620 patients randomized 1:1:1 as described in the Methods will yield 90% power if the exacerbation rate ratio is 0.70 (brensocatib over placebo) between either of the brensocatib treatment arms and placebo after 52 weeks of treatment. This estimate is based on study wise 2-sided type I error of .01 (or .005 for each primary comparison between brensocatib and placebo). Randomization will be stratified based on geographic region (North America, Europe, Japan, and the rest of the world), the presence of absence of *Pseudomonas aeruginosa* in a sputum sample at screening, and number of exacerbations (2 or ≥3) in the previous 12 months.

CONCLUSIONS

Treatments that reduce the frequency of exacerbations are urgently needed for patients with NCFBE. The results from the phase 2 WILLOW study showed that brensocatib reduces the risk of exacerbations through reduction of NE activity. The global phase 3 ASPEN study will evaluate the impact of brensocatib over 52 weeks on frequency and severity of exacerbations, as well as safety and tolerability in patients with NCFBE.

FUNDING: Insmed Incorporated, Bridgewater, NJ, USA

P.04 The prevalence of eosinophilic bronchiectasis defined by blood and sputum eosinophil counts: an EMBARC analysis

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Introduction: Bronchiectasis is classically considered an neutrophilic inflammatory disease. It has recently been suggested that a subset of patients with bronchiectasis have eosinophilic inflammation reflected in an elevated blood eosinophil count. The role of eosinophils in COPD and asthma is already recognised but the prevalence of the eosinophilic endotype of bronchiectasis without co-existing asthma or COPD is unknown.

Methods: Retrospective analysis of datasets held by the European Bronchiectasis Network (EMBARC) collaborative group, the FRIENDS dataset, BRIDGE study and individual single centre studies where data on blood eosinophil counts were available. Patients with a recorded co-diagnosis of asthma or COPD were excluded. A blood eosinophil count greater or equal to 300cells per ul was used as the definition of eosinophilic bronchiectasis. Blood and sputum eosinophils were correlated in two single centre datasets (Newcastle and Dundee, UK) to validate the use of blood eosinophil counts as a surrogate of eosinophilic inflammation.

Results: 112 and 123 patients were included in the Newcastle and Dundee datasets correlating sputum with blood eosinophil counts. The area under the receiver operator characteristic curve for blood eosinophils, where the dependent variable was a sputum eosinophil count >3%, was 0.68 95% CI 0.56-0.79,p=0.003 for the combined dataset indicating moderate discrimination (accuracy 67% in Dundee and 72% in Newcastle respectively).

The prevalence of elevated blood eosinophil counts varied from 18.0% to 29.5% across the datasets. (figure 1).

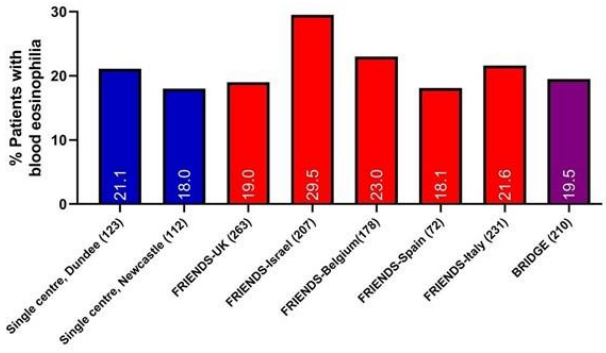

Figure 1. X axis shows the name of the dataset and N numbers per database.

Conclusion: Blood eosinophil counts may be a surrogate of sputum eosinophilia in NCFB. “Eosinophilic bronchiectasis” affects approximately 18-30% of patients without a known asthma or COPD diagnosis. This study is limited by retrospective design and further research is needed to understand the clinical implications.

P.05 Mycobacterium chimaera with pulmonary and lymphatic involvement in an immunosuppressed patient: a case report

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Background. *Mycobacterium chimaera* is a ubiquitous water-borne, slow-growing Non-Tuberculous Mycobacterium (NTM) belonging to the *Mycobacterium avium complex* (MAC). *M. chimaera* infection is rare and has become a global public health concern due to reported invasive outbreaks related to cardiac surgery. Presently, data on *M. chimaera* infection are mainly related to cardiothoracic surgery and very few data are available in immunocompromised patients. Overall, the identification of slow-growing NTM species is based on molecular techniques not largely available in healthcare facilities leading to possible delay in diagnosis and treatment.

Methods. Herein, we report a case of *Mycobacterium chimaera* infection in an immunocompromised patient admitted to the Department of Infectious Diseases at an academic hospital in Rome, Italy.

Results. In April 2019, a 38-years-old woman was admitted to our ward after a 2-week history of persistent dry cough. She was affected by Caroli disease and Mixed Connective Tissue Disease, the latter treated with chronic low-dose prednisone (5 mg/day) since 2015. A diagnosis of pulmonary *M. intracellulare* was performed in 2015 but two relapses further occurred in 2016 and 2017: the treatment prescribed was a combination of rifampin, isoniazid, pyrazinamide, clindamycin, prulifloxacin, rifabutin. Furthermore, in 2017 the patient underwent a left-hepatectomy because of the Caroli disease. At the time of the admission a culture from brochoalveolar lavage (BAL) was performed and a NTM was isolated, but the species identification was unsuccessful. A further *M. intracellulare* relapse was suspected and a combination treatment with azithromycin, ethambutol, pyrazinamide and rifampin was started and the patient was discharged after 3-week hospitalization. By the end of May 2019, a lymphadenitis in right supraclavicular-sternal region appeared, leading to skin fistulisation two months later (July 2019). Then, in September 2019 the patient was readmitted to our ward and a skin biopsy of the sternum was performed. A Polymerase-Chain Reaction (PCR) (GenoType NTM-DR, ARNIKA) for NTM identification was performed on the skin biopsy leading to the identification of a macrolide-resistant *M. chimaera*. Thus, chronic low-dose prednisone therapy was discontinued and the patient started an antibiotic therapy based on a combination of moxifloxacin, rifampin, ethambutol and linezolid. A month later the patient was discharged in good clinical condition (figure 1). After two weeks, moxifloxacin was stopped because of adverse event (skin rash) and replaced by a 4-week course of amikacin after which the patient continued the treatment with rifampin, ethambutol and linezolid. After one year of treatment, the patient showed a clinical and radiological improvement without additional adverse events related to the ongoing therapy.

Conclusion. We describe a misdiagnosed case of *M. chimaera* infection with pulmonary and lymphatic involvement. *M. chimaera*, together with *M. intracellulare* and *M. avium*, belong to MAC, but its treatment and prognosis are particularly challenging. *M. chimaera* infection is possibly misreported as *M. intracellulare,* leading to risk of low efficacy and appearance of drug-resistance, as in our immunosuppressed patient. Thus, molecular species identification through specific PCR assay is essential in order to better tailor the therapy to increase the chances of success against this difficult-to-treat infection.

P.06 Retrospective analysis of mycobacterial screening in cystic fibrosis patients in a tertiary hospital - rise and relevance of Mycobacterium chelonae

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Background/aims

Diagnosing NTM-PD (non-tuberculous mycobacteria pulmonary disease) in CF (cystic fibrosis) is challenging. Hence, NTM infections are underreported. Nevertheless, infections with *M. abscessus complex* and *M. avium* have been associated with accelerated pulmonary function decline in CF. The clinical significance of other NTM species like *M. chelonae* is unknown. Our objective was to describe how mycobacterial screening practices in CF impact NTM-PD diagnosis and treatment. Secondly, we wanted to assess the relevance of *M. chelonae* isolation from respiratory tract samples in CF.

Methods

We conducted a retrospective review of medical and laboratory records of all adult CF patients followed in the reference CF center of the University Hospitals Leuven between January 2015 and August 2020. Surveillance mycobacterial cultures were performed at least annually (six-monthly since 2017), unless clinical suspicion or a prior positive culture dictated more frequent testing. Mycobacterial cultures were performed on liquid medium (Bactec MGIT, Becton Dickinson, USA), and from 2017 onwards in parallel on solid medium (RGM medium, subsequently NTM Elite Agar, bioMérieux). Data collected were number of cultures, culture positivity rate, and isolated species over time and per patient. We compared baseline patient characteristics, treatment decisions and outcome variables of patients with at least one positive *M. chelonae* culture and NTM-negative patients.

Results

Between January 2015 and August 2020, 1813 respiratory samples from 267 patients were cultured for mycobacteria: 249 cultures from 102 patients in 2015-2016, and 1564 cultures from 241 patients in 2017-2020 (Figure 1). Overall culture

positivity rate was 10,4%; contamination rate was significantly lower with solid medium (1,34% vs 44,81%).

Most common species isolated were *M. abscessus complex* (n=60), *M. chelonae* (n=55), *M. chelonae-abscessus complex* (n=29) and *M. avium* (n=21), with *M. chelonae* mainly isolated from 2018 onwards.

Over time, a significantly higher percentage of the 267 CF patients tested positive for NTM (4,90% vs. 22,41%). In 2015-2016, 4/5 patients with positive NTM culture had *M. chelonae-abscessus complex* (with subsequently 2/4 identified as *M. abscessus* complex), whereas in 2017-2020 31/54 had *M. chelonae,* 8 of whom had at least 2 identical species isolated (Figure 2). Twenty-four percent had more than one positive sample.

M chelonae positive patients submitted more samples for mycobacterial culture than NTM-negative patients but otherwise did not differ in baseline characteristics or outcome variables (Table 1). The median time of follow-up since first isolation of *M. chelonae* was 411 days. FEV1 declined on average with 0,27 L or 9,15%. Mean annual exacerbation frequency was 0,71. No patient was started on antimycobacterial treatment for *M. chelonae* despite 8 (29,63%) fulfilling ATS/IDSA criteria.

Conclusions

With more frequent NTM screening and the use of more selective and performant culture media, a significantly higher percentage of CF patients had a positive NTM isolate over the past 5 years. New species, such as *M. chelonae*, have emerged, the reason for which is not entirely clear. To date, *M. chelonae* has been regarded a less pathogenic NTM. However, further longitudinal study of pulmonary function decline, exacerbation frequency and radiological imaging is required to judge the clinical relevance of this species.

BEST E-POSTER

P.07 Association between bronchiectasis and coronary artery calcium in an Australian cohort

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Background

Coronary artery calcium (CAC) scoring predicts cardiovascular risk in patients with traditional risk factors (smoking, previous cardiovascular disease, hypertension, hypercholesterolemia). Patients with bronchiectasis have chronic systemic inflammation that might contribute to CAC and hence may be a risk factor for ischaemic heart disease.

Methods

We retrospectively reported CAC scores on the CT scans of patients with bronchiectasis from our local

health district enrolled in the Australian Bronchiectasis Registry between 2016 and 2018. Patients were risk stratified for coronary artery disease on the basis of CAC scores. CT scans performed with contrast as a CT pulmonary angiogram were not suitable for CAC scoring. Bronchiectasis severity was calculated using the FACED score. Statistical analysis was performed using SPSS software. Somers'd test was used to assess the association between FACED score and CAC risk group, with FACED group as the independent variable.

Results

Of the 298 patients who were enrolled in the registry, 97 (72 female, mean age 65 ± 17y) had CT scans available that were suitable for CAC scoring. Mean body mass index of the cohort was 25 ± 6 kg/m^2. 74% were never smokers. 67% had no history of any cardiovascular disease. Severity of bronchiectasis based on FACED score was mild in 54% of the patients, moderate in 35% and severe in 11%. In terms of CAC risk stratification, 48% of patients had very low risk, 25% had low risk, 11% had intermediate risk, 3% had moderately high risk, and 12% had high risk of death from coronary artery disease. The rate of smoking was significantly higher in patients with higher CAC and FACED scores. There was a weak positive association between FACED score and CAC risk score, which was statistically significant d=0.188, p=0.045. When patients with smoking history were removed from the analysis, there was no significant association.

Conclusions

In this small study of patients with bronchiectasis, FACED score is weakly associated with severity of coronary artery calcification. Most of the CT scans performed in those with most severe bronchiectasis were unsuitable for retrospective CAC scoring and thus may underestimate the potential contribution of FACED severity to coronary artery risk. Smoking history remains a major contribution to CAC score.

P.08 Successful antimycobacterial oral treatment in Mycobacterium abscessus abscessus pulmonary infection during Covid-19 pandemic period: a valid approach based on the molecular and phenotypic sensitivity profile.

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Background: Mycobacterium abscessus is a formidable and difficult-to-treat mycobacterial pathogen with mutlidrug resistence mechanisms such as the presence of an inducible erythromycin methylase (*erm*) gene that confers macrolide resistence. M. abscessus can be split into three sub-species (M. abscessus, M. massiliense, M. bolletii) based on the

16SrRNA gene sequence and the presence or absence of the functional *erm* gene. We discussed the complexities involved in mycobacterial species/subspecies identification and the relative pharmacological approach expecially during COVID-19 pandemic period.

Case presentation: a 71-year-old man, was a retired teacher and was referred to our Infectious Diseases Day Hospital (DH) service for one month history of intermittent productive cough, asthenia, fever (38°C). He didn't use substances, drugs or nose drops. Chest radiograph showed a diffuse micronodular-bronchiectatic pattern and a consolidation in the right lower lobe of the lung. Laboratory datas, including lymphocytes count, gammablobulin level, anti-HIV antibody level, were unremarkable and the patient resulted also Covid-19 free. Nevertheless high levels of fibrinogen (9oo mg/dl) and C-reactive protein (25 mg/dl) were apparent. Microbiological cultures from sputum were negative while bronchial aspirates resulted positive for M. abscessus after 5 days of cultures. The M. abscessus was first identified directly by MALDI-TOF from rapid growing in Agar chocolate medium Acid-fast (Ziehl-Neelsen) staining positive colonies. INNO-Lipa thecnology as commercial DNA probes for Mycobacteria (Lypa Genotype Mycobacteria) analysis was further used to confirm the identity and subspecies as M. abscessus abscessus since a different paharmacological treatment should be done in relation to the M. abscessus subspecies. Moreover molecular genetic assay (GenoType NTM-DR version 1) for the detection of resistence to macrolide (*erm* gene) and aminoglycosides from cultured material was carried out. This gene provides intrinsic resistence to macrolides, so that different patterns lead to different treatment outcomes. The results showed a resistant macrolide profile due to the genotype t28 for *erm(41)*. Drug susceptibility in vitro testing for M.abscessus was also carried out in microdilution broth MH by Sensitrite RAPMYCOI system in order to check the sensitivity to macrolide, fluorochinoloni and others. Results showed a sensitivity for amikacin, cefoxitin, Imipenem, linezolid and tobramycin while resistence was found for ciprofloxacin, moxifloxacin, doxycyline, clarithromycin and Trimet/sulfa. Due to the heavy pandemic situation the patient was discharged after 3 days from our day service and we decided for an oral antibiotic treatment with cefaclor 750mg x2 die, linezolid 300 mg x2 die and azithromycin 500 mg. After 6 months of therapy the patient referred no problems, flogosis index were negative and the micronodular pulmonary pattern showed by HRTC was highly resolved.

Conclusions: Here we have described the feasibility, cost acceptability management, of a patient with M. abscessus abscessu pulmonary infection highly responsive to an oral treatment without hospitalization. This pharmacological approach without hospitalization, could be used as example especially during COVID-19 pandemy. A correct laboratory processing and reporting procedures for especially M. abscessus subspecies identification are necessary to identify intrinsic

resistence since different subspecies lead to different treatment outcome. The susceptibility testing with adequate phenotypic andmolecular techniques can result an important strategy in patient's clinical follow up in a pandemic situation. Any treatment decision should include adequacy to the specific practice clinical guidelines and the improvement of patient's quality of life.

P.09 Medication delivery of bronchiectasis drugs via a breath actuated nebulizer (BAN): Review of delivery performance versus a breath enhanced nebulizer (BEN) commonly used with such medications

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INTRODUCTION:

Medications to manage care of bronchiectasis patients are often delivered via a nebulizer, as such treatment is generally easy to use and enables delivery of the typical doses needed. A breath actuated nebulizer will reduce fugitive emissions and provide dose assurance (because dosing is not dependent on breathing pattern), however there are sometimes questions around the dose delivered to the patient when changing between continuous and breath actuated delivery modes. This study compares the two delivery modes for bronchiectasis medications commonly used in the home.

METHODS:

Three different medications were evaluated. These were: a) 7% hypertonic saline, b) Tobramycin, and c) Colistimethate Sodium. Delivery was compared for each with a breath actuated nebulizer (AEROECLIPSE* XL BAN / Ombra* compressor, Trudell Medical International) and continuous breath enhanced nebulizer (LC Plus BEN / PARI BOY SX compressor, PARI). Medication delivery was compared for each, from existing laboratory studies, in terms of the performance measures in each study.

RESULTS:

For hypertonic saline, the BAN exhibited an 81.6% fine droplet fraction compared to 71.2% with the BEN, indicative of slightly smaller droplets, more likely to be delivered to the lungs.

For Tobramycin, the BAN again exhibited a slightly higher fine particle fraction than the BEN (72% v 64%) and delivered a total mass of 141mg compared to 83mg for the BEN.

For Colistimethate, the fine droplet mass for the BAN was similar to the BEN for the first 12 mins of delivery, with the BAN continuing to deliver medication for an additional 7 mins.

CONCLUSIONS:

Although the medication delivery in the various lab studies was reported using differing metrics, a common trend was that the BAN delivered at least as much or more medication than the

BEN in each case. Reviewing the safety data for the drugs themselves shows that the higher delivery with the BAN was well within acceptable dosing ranges. Clinicians could recommend BAN for delivery of bronchiectasis medications on the basis of these studies.

BEST E-POSTER

P.10 Clinical characteristics of adult patients with bronchiectasis (Bx) and suspected primary ciliary dyskinesia (PCD) in Ukraine

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While PCD patients build a specific clinical phenotype and PCD accounts for up to 13% among causes of Bx in adults by world data, PCD testing is not available in routine clinical practice and there is no information on the prevalence of PCD and on the characteristics of these patients in Ukraine. **The study aimed** to define the prevalence of patients with suspected PCD as a cause of Bx and the microbiological profile of sputum of these patients in Ukraine.

Materials and methods. Data from all patients who visited our Bx outpatient Dnipro clinic from November 2018 until March 2021 were retrospectively analyzed from our database. PICADAR score (PrImary CiliAry DyskinesiA Rule) were calculated to identify potential patients for further PCD diagnosing. nNO was measured by NIOX Vero in stable phase, the level of 257 ppb (77 nL/min^{-1}) was considered as cut-off. Isolation and identification of pathogens were conducted by classical bacteriological methods of inoculation on nutrient media. The methods of descriptive and non-parametric statistics were used to process the results.

Results. After the initial analysis of the cohort (84 patients) on the PICADAR scale, 20 patients were included in the further study. The age of patients ranged from 23 to 67 years, the median - 37 (34; 44) years, five - men (25%). The level of nNO ranged from 5 to 660 ppb, the median - 131 (19; 339) ppb.

13 patients had nNO<257 ppb and were determined as patients with suspected PCD (15.5 % from the whole cohort and 65 % from tested for PCD patients). Their age was from 23 to 61 years, the median 37 (36; 44) years, they were statistically significantly younger than non-PCD Bx patients (p=0.0006 by Mann-Whitney test). Three were men (23.1 %). Two women have situs inversus (15.4 %). Five of these patients (38.7 %) had frequent exacerbations (FE) and this rate was statistically equal to the non-PCD Bx patients (32 from 71 had FE – 45 %, p=0.65 by xi-square test). Five of them had chronic colonization of sputum with *Pseudomonas aeruginosa* (38.7 %) in comparison with 11 patients from 55 non-PCD Bx patients produced sputum (20 %), but this difference was not statistically significant (p=0.29 by xi-square test).

Conclusions. The prevalence of patients with suspected PCD among study population was 15.5%. These patients were younger than their counterparts, but their age indicates a significant diagnostic delay. We did not detect statistically significant difference in *Pseudomonas aeruginosa* colonization prevalence and the number of frequent exacerbators between suspected PCD patients and non-PCD Bx patients, but there is a need for further research in a larger study population.

P.11 Treatment regimen appropriateness for patients enrolled in Italian Registry on Pulmonary Non-Tuberculous Mycobacteria (NTM) - IRENE

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Background: The Italian Registry on pulmonary Non-Tuberculous Mycobacteria or NTM (IRENE) has been set up in April 2017 as an observational, multicenter, prospective, cohort study enrolling consecutive adults with active NTM pulmonary infection or disease (NTM-PD) from 57 Italian centers. Data are collected at baseline with yearly follow-up visits.

Aims: To evaluate the appropriateness of therapeutic regimens of NTM-PD IRENE patients in comparison with the recommendations of the Official ATS/ERS/ESCMID/IDSA Clinical Practice Guidelines, 2020, focusing on the most incident NTM species (*Mycobacterium Avium Complex* - MAC*, M. kansasii, M. abscessus,* and *M. xenopi*).

Methods: Eleven indicators (1 general, 3 for MAC and *M. kansasii*, 2 for *M. abscessus* and 1 for *M. xenopi*) were used to evaluate the proportion of NTM-PD patients started on treatment and the adherence with the recommendations (Table 1). Results were satisfactory if ≥80% was treated in line with the recommendations. Data validated as of 15th June 2020 were selected.

Results: 517 patients were enrolled during the study period. 370 (71.6%) had NTM-PD and were included in the analysis. Median (IQR) age was 67 (53-75) years, 70.0% were females, median (IQR) BMI was 21.0 (18.9-22.9), and 46.0% were current/former smokers. Bronchiectasis (67.0%),

COPD (20.5%), and cystic fibrosis (10.5%) were the most frequent pre-existing lung diseases. The most prevalent NTM were MAC (267/370, 72.2%), *M. abscessus* (53/370, 14.3%), *M. xenopi*(15/370, 4.1%), and *M. kansasii* (13/370, 4.1%). 77.3% had cough, 55.4% sputum production, 50.8% fatigue, 47.0% shortness of breath, 36.5% weight loss, 42.7% intermittent fever, 26.5% hemoptysis, and 23.0% night sweats. 21.1% had cavitating nodules, 12.7% large cavities, and 58.4% consolidations. 284/370 (77.0%) patients with NTM-PD underwent treatment, including azithromycin/clarithromycin, ethambutol, rifampicin/rifabutin. Out of the 275 patients with NTM-PD caused by MAC, *M. abscessus*, *M. xenopi* or *M. kansasii* who were treated, 226 (82.2%) received treatment regimens in line with recommendations. Details are provided in Table 1.

#	Indicator	N	%
1	NTM-PD enrolled on treatment/NTM-PD	284/370	(77.0%)
2	MAC PD enrolled on treatment	222/267	(83.1%)
3	*M. abscessus* PD enrolled on treatment	32/53	(60.4%)
4	*M. kansasii* PD enrolled on treatment	11/13	(84.6%)
5	*M. xenopi* PD enrolled on treatment	10/15	(66.7%)
6	MAC PD treated with a macrolide containing regimen	216/222	(97.3%)
7	MAC PD treated with at least three drugs, including a macrolide	185/222	(83.3%)
8	*M. abscessus* PD treated with at least three drugs	31/32	(96.9%)
9	*M. kansasii* PD treated with rifampin, isoniazid and ethambutol	4/11	(36.4%)
10	*M. kansasii* PD treated with rifampin, isoniazid and macrolide	0/11	(0.0%)
11	*M. xenopi* PD treated with rifampin, ethambutol, macrolide and/or FQ	6/10	(60.0%)

Conclusions: A high proportion of NTM-PD was treated and satisfactory level of adherence with treatment recommendations was detected, especially for the NTM-PD caused by the most common species (MAC and *M. abscessus*), whereas indicators for *M. xenopi* and *M. kansasii* showed gaps.

No conflicts of interest reported.

P.12 Risk factors for non-tuberculous mycobacterial pulmonary disease in France based on health claims database analysis

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Introduction:

Nontuberculous mycobacterial lung disease (NTMLD) affects mostly susceptible individuals and is rare but increasing in prevalence. Timely and accurate diagnosis is crucial for optimal patient care and improving outcomes.

Objective:

The aim of this study was to identify host-related risk factors associated with NTMLD in France.

Methods:

A retrospective analysis was performed using the SNIIRAM database over 2010-2017. Patients with NTMLD were identified based on the ICD10 codes during hospitalizations and / or specific antibiotics treatment regimens. The study population was matched (age, gender and region) to a control group (1: 3) without NTMLD. Both groups were compared for prevalence of risk factors and odds ratios (OR) were calculated in a multivariate logistic regression model.

Results:

A total of 5,628 patients with NTMLD (men: 52.9%) were identified over the study period. Pulmonary diseases were more prevalent in the cohort with NTMLD diagnosis, and the most common conditions were pneumonia (24.8% for NTMLD / 1.4% for controls), followed by COPD (18.9% / 1.2%) and bronchiectasis (10.6% / 0.1%) .

Commonly used drugs by NTMLD patients were proton pump inhibitors (64.8% / 42.0%) followed by corticosteroids (55.4% / 29.9%), inhaled corticoids (23.8% / 7.8%) and azithromycin (20.5% / 7.8%). Malnutrition and smoking were all more common in the NTMLD group compared to controls, with difference of 20.1%, and 11.4%, respectively.

In the multivariate analysis, the three highest significant odds ratios (ORs) were for the history of tuberculosis (OR = 705, 95% CI: 95-5,228), bronchiectasis (OR = 226, 95% CI: 48-1,065), and cystic fibrosis (OR = 130, 95% CI: 17-984), all of which were present in more than 5% of NTMLD patients. (Table 1)

Conclusions:

Whereas screening for NTM is recommended in guidelines for bronchiectasis and cystic fibrosis, this study provides insights into other high-risk groups. Further studies should be conducted in order to confirm the association between those newly identified risk factors and NTMLD.

Table 1. Frequencies of risk factors and odds ratios based on multivariate logistic regression analysis

Risk factors	NTMLD group (%)	Control group (%)	Difference (%)	Odds ratio (mean, 95% CI)*
Co-morbidities				
COPD	18.9	1.2	17.7	11.7 (7.3-18.7)
Bronchiectasis	10.6	0.1	10.5	226.4 (48.1-1065.2)
HIV	7.5	0.2	7.3	112.7 (36.3-349.5)
History of tuberculosis	7.1	<0.1	7.1	705 (95.1-5227.1)
Chronic bronchitis	6.9	0.5	6.4	15.8 (6.8-36.7)
Asthma	6.5	0.9	5.6	3.1 (1-9.7)
Lung cancer	3.6	0.3	3.3	14.6 (8.9-23.9)
Organ transplantation	2.9	0.1	2.8	57 (6-545.2)
Cystic fibrosis	2.6	<0.1	2.6	130.3 (17.3-983.7)
Idiopathic pulmonary fibrosis	2.4	<0.1	2.4	43.4 (11-171.6)
Rheumatoid arthritis	2.0	0.2	1.8	10.2 (2.5-41.4)
Primary ciliary dyskinesia	1.2	<0.1	1.2	70.3 (5.6-885.4)
Drugs				
Proton pump inhibitors	64.8	42.0	22.8	1.5 (1.2-2.0)
Corticoids	55.4	29.9	25.5	NS
Inhaled corticoids	23.8	7.8	16.0	1.7 (1.2-2.6)
Azithromycin	20.5	7.8	12.7	2.1 (1.4-3.1)
Colistin	3.5	<0.1	3.5	48.4 (5.9-398.6)
Leflunomide	0.5	<0.1	0.5	9.5 (1.4-63)
TNF alfa inhibitors	0.5	0.1	0.4	3.5 (1.3-9.8)
Other factors				
Malnutrition	22.1	2.0	20.1	43.1 (14.7-126.8)
Smoking	13.6	2.2	11.4	NS

* Multivariate analysis

P.13 Case series: patients with allergic bronchopulmonary aspergillosis (ABPA) treated with dupilumab

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BACKGROUND

Allergic bronchopulmonary aspergillosis (ABPA) is caused by chronic allergic inflammation triggered by inhaled fungal spores. ABPA can occur in patients with asthma or cystic fibrosis, causing dyspnea, cough and frequent exacerbations and leading to bronchiectasis and lung function decline. The disease is characterized by both high IgE levels and high eosinophil counts. Cornerstones of treatment have been systemic steroids and azole antifungals, although treatment protocols have not been investigated extensively. Dupilumab is a biological agent with IL-4 and IL-13 antagonistic properties, counteracting IgE producing B-cells and eosinophils. Dupilumab efficacy in non-CF ABPA has been observed in two small studies (Ramonell et al. 2020, Corren et al. 2019). Here we document our experience with dupilumab for patients with ABPA and underlying asthma.

METHODS

Retrospective case series. All patients provided written informed consent. After institutional approval, relevant parameters were collected in a dedicated database. Comparisons were made between 6 months prior and 6 months after first dupilumab dose.

RESULTS

Baseline: Six patients were identified. Median age 76 years (61-83 years), five out of six male. All patients had a history of allergic asthma. All patients had ABPA diagnosis (ISHAM 2013 criteria) for at least one year, in two patients more than 10 years. All patients had a history of oral prednisone treatment and five out of six patients were on maintenance oral prednisone (7.5 or 10mg/day) at baseline. Five out of six patients had a history of azole treatment. Three patients had been treated with omalizumab. All patients used ICS and dual bronchodilators. Median FEV1 before dupilumab was 76.5% predicted (27-96.3%) and median total IgE was 1921 kU/L (66-4147 kU/L). All patients had bronchiectasis, median modified Reiff score 4.5 points (2-13 points). One patient had concurrent infection with *Pseudomonas aeruginosa*. **Treatment**: All patients started dupilumab between March 2019 and July 2020. Maintenance dose was 300mg every two weeks. **Efficacy**: After start of dupilumab, five out of six patients reported a subjective improvement. Four out of six patients had a documented increase in FEV1.

The number of exacerbations for which additional steroids were prescribed decreased in five out of six patients, with median 2.5 (1-4) exacerbations in the six months pre-dupilumab and median 0 exacerbations (range 0-1) in the six months post-dupilumab. Three patients had a documented fall in total IgE below 1000 kU/L. After six months of dupilumab treatment, oral prednisone was discontinued in two out of five patients. Prednisone dose was continued in reduced dose in three out of five patients, of whom one had steroid withdrawal syndrome and one had discontinued dupilumab. Not all follow-up parameters were available due to the retrospective design. **Safety**: Dupilumab was discontinued in one patient because of complaints of arthralgia.

CONCLUSIONS

In this retrospective cohort of six patients with ABPA and asthma treated with dupilumab, improvements were observed in symptoms, FEV1, exacerbation frequency, maintenance prednisone and total IgE. Dupilumab may be an effective alternative to steroid/azole treatment in ABPA.

DISCLOSURE

All authors declare no conflict of interest.

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