Characterizing patients with moderate-to-severe asthma with preserved small airway function

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with severe asthma experience comorbidities treatable with specific MAbs.[9]

Retrospective assessment and BARS agreed in 76% to 86% of cases. Consequently, the κ rating grew from "moderate" in initial therapy to "substantial" for subsequent therapies.[10] Positive agreement between RA and BARS was almost 100%, showing BARS ability to correctly identify responders. Nonresponders were less likely to be coidentified; ie, patients were BARS but not RA responders.

Although BARS distinguishes 3 categories, this could not be implemented in RA.[7] For correlation, BARS results were categorized into "responders" and "non-responders," possibly limiting the evaluation of BARS' full potential. Nonetheless, our study suggests that BARS supplements the individual physician's subjective assessment (ie, RA), the current "gold standard," with standardized responder criteria. BARS only allows efficacy-based therapy assessment, without incorporating other considerations.[7] Therefore, MAb switches for causes other than inefficacy were excluded from RA/BARS correlation, limiting the comparison but reflecting real-world challenges in severe asthma therapy. Furthermore, retrospective analysis has drawbacks, including the limitation to an existing dataset instead of patient recruitment to meet a precalculated power level.

In summary, switches in MAb therapy are common and often successful in patients with severe asthma when the response to 1 or more previous MAb therapies was unsatisfactory. BARS largely matched the clinical observations of physicians and can be a helpful tool in assessing MAb therapy response and the need for therapy switches.

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Characterizing patients with moderate-to-severe asthma with preserved small airway function

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The small airways are termed the quiet zone of the lung due to the considerable challenges faced by clinicians when trying to assess and treat disease in this area. Small airway dysfunction (SAD) can be quantified using forced expiratory flow rate between 25% and 75% of forced vital capacity ($FEF_{25\%-75\%}$) with spirometry or using heterogeneity in resistance between 5 Hz and 20 Hz (R5-R20) and reactance area (AX) with airway oscillometry (AO). According to the ATLANTIS study,[1] between 35% and 80% of patients with Global Initiative for Asthma–defined moderate-to-severe asthma exhibit spirometry- or AO-defined SAD. Here, the wide range of patients with associated SAD likely reflects the clinical heterogeneity of asthma pathophysiology and differences in pulmonary function modality. Owing to a

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paucity of research, we endeavored to describe characteristics associated with patients with moderate-to-severe asthma who have preserved small airway function.

Data on 215 patients with Global Initiative for Asthma–defined moderate-to-severe asthma attending our National Health Service secondary care asthma clinic were retrospectively collected. Here, preserved AO was defined as patients who exhibited both R5-R20 less than 0.10 kPa/L/s and AX less than 1.0 kPa/L, whereas for preserved spirometry, it was an $FEF_{25\%-75\%}$ greater than or equal to 60% predicted.[2,3] The number of severe annual exacerbations requiring oral corticosteroids was retrieved from medical records, whereas symptom control was assessed using the Asthma Control Questionnaire (ACQ). AO was measured before spirometry using Impulse Oscillometry MasterScreen (CareFusion, Hoechberg, Germany) according to the European Respiratory Society technical standards. Spirometry (Micromedical, Chatham, United Kingdom) was performed according to international guidelines. Fractional exhaled nitric oxide (FeNO) measurements were taken using NIOX VERO (Circassia, Oxford, United Kingdom) according to the manufacturer's instructions and American Thoracic Society guidelines. All type 2 (T2) biomarkers (peripheral blood eosinophils, FeNO, and total immunoglobulin E) were obtained before biologic initiation. Caldicott approval (IGTCAL10018) was obtained before data collection. Formal statistical comparison between the AO and $FEF_{25\%-75\%}$ groups was not feasible due to a substantial overlap of patients, although inspection of 95% CIs may infer distribution heterogeneity.

Table 1 portrays the demographics, pulmonary function, asthma control, and T2 biomarker data for patients with asthma who had preserved AO, spirometry, or both. Of 215 patients, 75 (35%) and 77 (36%) exhibited preserved small airway function defined by AO and spirometry, respectively, whereas 47 (22%) had both preserved AO and spirometry. Our results indicate that in patients with preserved small airway function, there remains a persistent level of disease activity with 60% having poor control defined by ACQ greater than or equal to 1.5 and 40% having frequent exacerbations (≥2 per year) in those with preserved AO and a corresponding 66% and 36% in those with preserved $FEF_{25\%-75\%}$.

Previous data evaluating all severities of asthma revealed a prevalence of normal small airway function in the region of 46% for $FEF_{25\%-75\%}$ greater than or equal to 60%[4]; 58% for R5-R20 less than 0.10 kPa/L/s[4] and 67% for R5-R20 less than 0.075 kPa/L/s.[5] In our study of patients with more severe asthma requiring higher inhaled corticosteroid doses, it was therefore unsurprising that the prevalence of preserved small airway function was somewhat lower. Although most patients with preserved AO also had normal spirometry results using standard cut points of forced expiratory volume in 1 second (FEV_1) greater than or equal to 80%, $FEF_{25\%-75\%}$ greater than or equal to 60%, and FEV_1/forced vital capacity greater than or equal to 0.70, closer examination revealed that almost half (48%) exhibited an $FEF_{25\%-75\%}$ less than 60%. Researchers have also debated whether mid-expiratory flow is highly variable, but $FEF_{25\%-75\%}$ displays good repeatability in severe asthma and now has an established biological variability value.[6] This disconnect between AO and $FEF_{25\%-75\%}$ provides additional insight into why combining conventional spirometry with AO leads to superior detection of patients with more frequent exacerbations and worse asthma control.[2]

It was also interesting to note that most patients with preserved AO (60%) or $FEF_{25\%-75\%}$ (66%) had poorly controlled symptoms denoted by a mean ACQ greater than or equal to 1.5. This might be explained by a priori selection of more severe patients along with greater levels of T2 inflammation within our cohort, which in turn, is associated with poorer asthma control.[7] When using cut points of peripheral blood eosinophil greater than or equal to 300 cells/μL, FeNO greater than or equal to 25 ppb, and total immunoglobulin E greater than or equal to 100 kU/L, there was a similar frequency of high or low T2 inflammation in each of the 3 groups. This in turn

Table 1
Demographics, Pulmonary Function, Asthma Control, T2 Biomarkers, and Prevalence of Clinical Associations

Clinical characteristic	R5-R20 < 0.10 kPa/L/s and AX < 1.0 kPa/L (n = 75)	$FEF_{25\%-75\%}$ ≥ 60% (n = 77)	R5-R20 < 0.10 kPa/L/s and AX < 1.0 kPa/L and $FEF_{25\%-75\%}$ ≥ 60% (n = 47)
Age (y)	49 (46-52)	45 (42-49)	46 (42-51)
BMI (kg/m^2)	28.7 (27.5-30.0)	32.0 (30.3-33.8)	30.5 (28.5-32.4)
ICS dose (μg)	1607 (1497-1717)	1690 (1445-1934)	1560 (1411-1708)
Sex (F/M)	41/34	56/22	33/14
Current smoker (%)	7%	5%	2%
ACQ	1.9 (1.6-2.2)	2.2 (1.8-2.6)	2.1 (1.6-2.5)
Exacerbations	1 (3)	1 (3)	1 (2)
FEV_1%	95.2 (90.8-99.6)	101.9 (98.9-105.0)	105.8 (101.7-109.8)
$FEF_{25\%-75\%}$	65.2 (58.2-72.3)	81.4 (77.3-85.5)	86.3 (80.3-92.4)
FVC%	108.9 (105.5-112.3)	106.8 (103.3-110.2)	110.2 (105.9-114.6)
FEV_1/FVC	0.73 (0.70-0.76)	0.81 (0.80-0.82)	0.81 (0.80-0.83)
R5-R20 (kPa/L/s)	0.05 (0.04-0.05)	0.09 (0.07-0.11)	0.05 (0.04-0.06)
AX (kPa/L)	0.38 (0.32-0.43)	0.84 (0.59-1.09)	0.34 (0.28-0.40)
PBE (cells/μL)	318 (273-364)	302 (248-355)	281 (223-339)
Total IgE (kU/L)	423 (161-685)	319 (105-533)	374 (36-713)
FeNO (ppb)	38 (28-48)	30 (22-39)	32 (19-45)
BMI ≥ 30 kg/m^2	37%	60%	51%
FEV_1/FVC < 0.7	35%	1%	0%
FEV_1 < 80%	24%	5%	4%
$FEF_{25\%-75\%}$ < 60%	48%		
R5-R20 ≥ 0.10 kPa/L/s		35%	
AX ≥ 1.0 kPa/L		27%	
PBE ≥ 300 cells/μL	53%	46%	44%
FeNO ≥ 25 ppb	51%	36%	34%
Total IgE ≥ 100 kU/L	52%	47%	44%
ACQ ≥ 1.5	60%	66%	62%
Exacerbations ≥ 2/y	40%	36%	32%

Abbreviations: ACQ, Asthma Control Questionnaire; AX, area under reactance curve; BMI, body mass index; F, female; FEF_{25-75}, forced expiratory flow rate between 25% and 75% of FVC; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IgE, immunoglobulin E; M, male; PBE, peripheral blood eosinophil; R5-R20, heterogeneity of resistance between 5 and 20 Hz.
NOTE. Age, BMI, ICS dose, spirometry, oscillometry, T2 biomarkers, and ACQ as means (95% CIs). Severe annual exacerbations over the preceding year as medians (IQR).

perhaps explains why amalgamating pulmonary function values with T2 biomarkers also leads to superior detection of patients with asthma with worse clinical outcomes.[8]

Although statistical comparison between the AO and $FEF_{25\%-75\%}$ groups was not feasible due to a substantial overlap of patients, it was intriguing to note that those with preserved AO had numerically worse spirometry, whereas patients with asthma with preserved $FEF_{25\%-75\%}$ had numerically worse AO. This disconnect highlights the different aspects of pulmonary pathophysiology measured by each device. In addition, patients with preserved $FEF_{25\%-75\%}$ had a higher mean body mass index than those with preserved AO with non-overlapping 95% CIs. There was a 60% vs 37% relative prevalence of obesity for preserved $FEF_{25\%-75\%}$ and AO, respectively, perhaps supporting the notion that AO is a more sensitive test of distal airway mechanical compression.[9]

We recognize the potential limitations of the present study including its retrospective nature using data from a single specialist UK center. However, a paucity of literature in this area especially pertaining to more severe asthma might somewhat mitigate this. Furthermore, SAD occurs on a continuous spectrum, and therefore the use of putative cut points for $FEF_{25\%-75\%}$, R5-R20, and AX is an educated estimate. Nonetheless, compelling data exist supporting the use of such thresholds to signify severe SAD in patients with asthma.[10] Pragmatically, clinicians are also more likely to use memorable cut points in busy real-life practice rather than individual z-scores. Our data were cross-sectional in patients before receiving biologics, and hence, we would be interested to know whether the prevalence of preserved small airway function changes over time in patients with more severe asthma and how this might relate to altered T2 biomarkers during biologic therapy.

In conclusion, we describe an appreciable burden of abnormal disease control and raised T2 biomarkers in patients with moderate-to-severe asthma who have preserved small airway function defined by either AO or spirometry.

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"Let a sleeping dog lie": Perspectives from patients and clinicians about penicillin allergy delabeling

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Although penicillin allergy evaluation, with resultant "delabeling" as indicated, is recommended to reduce the impact of inaccurate penicillin allergies on care and antibiotic resistance,[1] most patients remain incorrectly labeled.[2] We performed a qualitative study to understand barriers and facilitators to penicillin allergy delabeling. Guided by the Theoretical Domains Framework, we conducted in-person in-depth interviews for clinicians and patients with penicillin allergy.[3] When needed, interviews in other languages used a telephone translator service. Interviews were recorded and transcribed. After developing a preliminary deductive codebook, it was revised based on a subsample of interviews[4,5] to include emergent themes. Recruitment ceased at the point of thematic saturation. The study was approved by the Tufts Health Sciences institutional review board.

We interviewed 32 individuals (21 patients and 11 clinicians) from May 2022 to December 2022. Interviews were conducted in-

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