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LETTER

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As a systemic form of therapy, it is perhaps intuitive to hypothesize that biologics would be able to penetrate the peripheral airways. However, there is a paucity of literature pertaining to the impact of biologic therapies on small airway dysfunction (SAD) in patients with more severe asthma. Airway oscillometry (AO) is an effort independent test that may be used to assess change in SAD.

Here we report on a post hoc analysis from two prospective phase IV clinical trials investigating the effect of anti-IL5Rα benralizumab (EudraCT 2019–003763-22) and anti-IL4Rα dupilumab (EudraCT 2021–005593-25) in patients with type 2 high poorly controlled severe asthma, where AO was a secondary end point.

Baseline demographics are shown in Table 1.

In the 22 patients with SAD defined by R5-R20, we observed a between-treatment difference in the mean relative %improvement (95% CI) from baseline for dupilumab versus benralizumab amounting to 44.2% (2.1,86.3) $p = .04$ for R5-20 and 42.6% (1.7,83.5) $p = .04$ for AX (Figure 1A). Corresponding differences between treatments for the 28 patients with SAD defined by AX were 44.5% (−0.9,89.9) $p = .054$ for R5-20 and 45.0% (8.7,81.3) $p = .02$ for AX (Figure 1B). For the absolute change in AO from baseline patients there were significant differences between treatments for R5-R20 but not for AX (Table S1).

We believe this to be the first ever post hoc case matched analysis, from two prospective studies, demonstrating superior efficacy with dupilumab compared to benralizumab on peripheral airway resistance and compliance using AO. Previous computational modeling identified a cut point for the R5-R20 exceeding 0.08 kPa/L/s to be a sensitive measure of severe SAD.[1] The fundamental premise here is that anti-IL4Rα therapy with dupilumab blocks IL-13 signaling, which is an integral cytokine involved in regulating bronchial

TABLE 1 Baseline patient demographics.

	Baseline R5-R20 ≥ 0.10 kPa/L/s ($N = 22$)		Baseline AX ≥ 1.0 kPa/L ($N = 28$)	
	Benra	Dupi	Benra	Dupi
Age (year)	55 (46,64)	59 (54,65)	56 (48,64)	59 (52,65)
BMI (kg/m^2)	32.1 (28.0,36.3)	31.2 (27.8,34.6)	31.2 (27.8,34.6)	31.3 (27.6,35.1)
Female (%)	45%	55%	50%	64%
ICS dose (μg)	1836 (1590,2083)	1273 (916,1630)**	1871 (1681,2061)	1257 (973,1542)***
FEV_1%	76.9 (64.3,89.5)	79.3 (67.4,91.2)	76.1 (64.8,87.4)	83.2 (74.9,91.6)
FEF_{25-75}%	38.9 (26.8,51.0)	39.7 (27.1,52.3)	37.9 (27.6,48.2)	40.9 (31.8,50.0)
FEV_1/FVC	66.2 (59.6,72.7)	64.3 (56.9,71.6)	65.9 (60.4,71.4)	66.3 (61.3,71.2)
R5-R20 (kPa/L/s)	0.22 (0.14,0.30)	0.22 (0.16,0.28)	0.19 (0.12,0.26)	0.17 (0.11,0.23)
AX (kPa/L)	4.36 (2.26,6.46)	4.62 (2.83,6.40)	3.79 (2.07,5.50)	3.55 (2.10,5.00)
FeNO (ppb)	57 (51)	57 (48)	39 (47)	47 (47)
PBE (cells/μl)	340 (280)	410 (270)	385 (293)	420 (238)
ACQ	2.6 (2.0,3.1)	2.4 (1.9,3.0)	2.5 (2.1,3.0)	2.4 (2.0,2.8)

Note: Baseline data for small airways dysfunction characterized by either R5-R20 or AX for benralizumab (Benra) or dupilumab (Dupi).FeNO and PBE are shown as medians (IQR), otherwise depicted as mean and 95% CI.

Abbreviations: ACQ, asthma control questionnaire; AX, as peripheral compliance as area under the reactance curve; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid as BDP equivalent dose; PBE, peripheral blood eosinophils; R5-R20, peripheral resistance heterogeneity between 5 and 20 Hz.

**$p < .01$, ***$p < .001$.

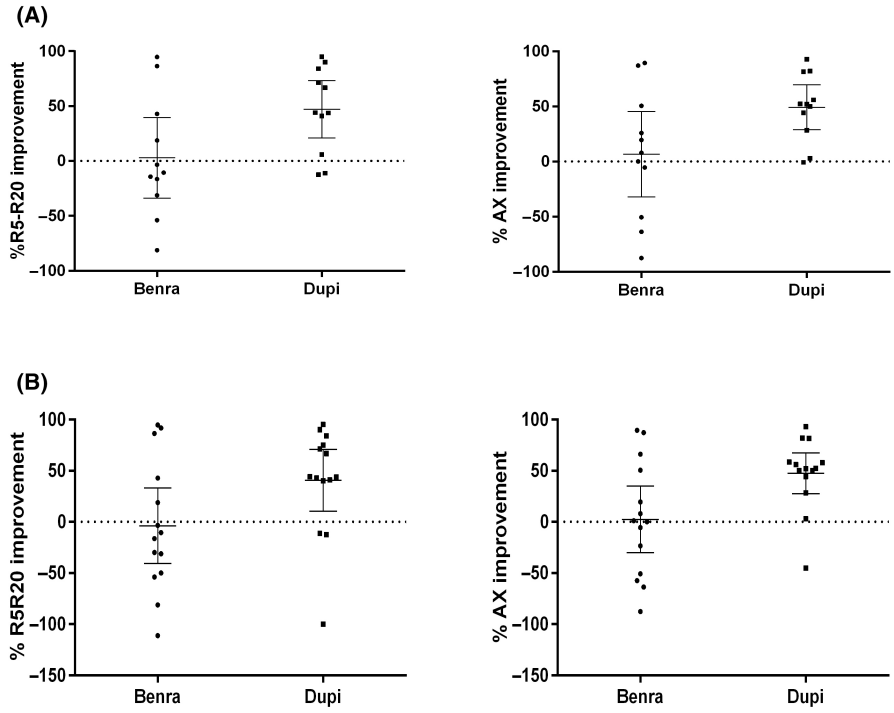

FIGURE 1 Individual data are presented as means and 95% CI for the within-treatment relative percentage improvement at 12 weeks from baseline for either R5-R20 or AX, treated with either benralizumab (Benra) or dupilumab (Dupi). (A) In 22 patients who were case matched for SAD defined by baseline R5-R20 ≥ 0.10 kPa/L/s. The differences between Benra versus Dupi were significant ($p < .05$) for both R5-20 and AX. (B) In 28 patients who were case matched for SAD defined by baseline AX≥1.0 kPa/L. The difference between Benra versus Dupi was significant ($p < .05$) for AX.

smooth muscle tone and airway geometry.[2] This was exemplified by the within-treatment response for dupilumab for R5-20 of 0.11 kPa/L/s and for AX of 2.46 kPa/L exceeding the intra-subject biological variability values of 0.04 kPa/L/s and 0.39 kPa/L for R5-R20 and AX, respectively in severe asthma, in turn inferring these improvements were likely to be clinical relevant.[3] Furthermore, AO appears to be more sensitive for detecting subtle changes in airway geometry since the between-treatment spirometry difference was not statistically significant (Table S1). For the between-treatment comparisons our findings for the relative mean percentage differences in R5-R20 of 44.2% and in AX of 42.4% exceeded the previously reported minimal importance differences of 37% and 41%, respectively.[4] Our observation validates a previous report demonstrating significant improvements in R5-R19 and AX with dupilumab alongside improvements in symptom control exceeding the MCID.[5] In this regard, we look forward to further results from the phase IV VESTIGE trial (NCT04400318) investigating the impact of dupilumab on AO-defined SAD as an exploratory outcome.

Our findings showing that benralizumab did not improve R5-R20 or AX are consistent with a previous report showing no improvements in the same outcomes after 24 weeks.[6] Interestingly, when comparing the biologics for the relative percentage improvement from baseline, there was considerably more heterogeneity for the within-treatment response to benralizumab than dupilumab (Figure 1).

We appreciate that interpretation of our study should be made in the context of potential limitations including data obtained from two studies performed in a single specialist UK severe asthma centre. However, the use of same methods, study protocols, and clinical trial staff for both studies allowed for a more homogenous comparison. The 95% CIs were relatively wide due to small patient numbers, albeit significant between treatment differences were still detected for peripheral airway resistance as either a percentage or absolute change from baseline. Pointedly, the primary outcome of both prospective studies was mannitol airway hyperresponsiveness. Both treatment arms were case matched according to baseline AO values to allow for similar potential room for improvement with either biologic so as not to bias the findings. The small airways are more closely associated with poorer symptom control, and therefore we hope the findings from our study can be used to support SAD as a treatable trait when choosing the optimal biologic. Prospective head-to-head biologic trials are now indicated to confirm our preliminary findings.

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CONFLICT OF INTEREST STATEMENT

Dr Chan reports personal fees (talks) and support attending ERS from AstraZeneca, personal fees from Vitalograph, and personal fees (talks) from Thorasys. Ms Stewart reports no conflicts of interest. Dr Kuo reports personal fees from AstraZeneca, personal fees from Chiesi, and nonfinancial support from GSK outside the submitted work. Dr Lipworth reports grants, personal fees (consulting, talks and advisory board), other support (attending ATS and ERS) from AstraZeneca; grants, personal fees (talks and consulting) from Sanofi/Regeneron, personal fees (consulting, talks and advisory board) from Circassia in relation to the submitted work; grants, personal fees (consulting, talks, advisory board), other support (attending ERS) from Teva, personal fees (talks and consulting), grants and other support (attending ERS and BTS) from uppleChiesi, personal fees (consulting and talks) from Lupin, personal fees (consulting) from Glenmark, personal fees (consulting, talks, advisory board), other support (attending BTS) from Boehringer Ingelheim, grants and personal fees (advisory board and talks) from Mylan outside of

the submitted work; and the son of BJL is presently an employee of AstraZeneca. The son of BJL is an employee of AstraZeneca.

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None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

INFORMED CONSENT STATEMENT

All participants gave informed consent prior to involvement in clinical trial related activities.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.