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Effects of dupilumab on quality of life burden in refractory type 2 high unified airway disease

To the Editor,

This is the first reported prospective analysis of both upper and lower airway outcomes, including quality of life, in patients with type 2 high (T2H) asthma and chronic rhinosinusitis with nasal polyposis (CRSwNP) who have unified airway disease (UAD) treated with dupilumab. Twenty-one participants with refractory T2H UAD taking inhaled and intranasal corticosteroid (ICS/INCS) were prospectively evaluated after an initial 4-week run-in at baseline, after 12 weeks of dupilumab 300 mg q2wk, and then following a 12-week washout period 14 weeks after the last dose of dupilumab at 24 weeks (EudraCT 2021–005593-25) (Table S1; Figure S1). Significant ($p < .001$) improvements in the following outcomes were found with dupilumab. Mean (95% CI) changes from baseline at 12 weeks in quality of life scores were: mini-AQLQ 2.36 (1.77–2.94) and SNOT22 43 (29–57); symptom scores: ACQ-6 1.80 (1.29–2.31), hyposmia VAS 5.35 (3.25–7.46); and changes in airflow at 12 weeks were: peak nasal inspiratory flow (PNIF) 44 L/min (23–65), peak expiratory flow (PEF) 60 L/min (30–90), and endoscopic nasal polyp score (NPS) 2.19 (1.72–2.66). (Table 1; Figure 1). Responder analysis for values exceeding the minimal clinically important differences (MCID's)[1–4] were: AQLQ 20/21 (>0.5), SNOT22 19/21(>9), ACQ-6 19/21(>0.5), Hyposmia VAS 15/21(>2.3), Nasal global VAS 17/21(>2.3), TNSS 18/21(>0.55), PNIF 17/21(>5 L/min), PEF 15/21(>19 L/min), and NP score 15/21(>1.0). For T2 biomarkers significant improvements were seen in nasal nitric oxide (nNO) and FeNO after 12 weeks while peripheral blood eosinophils (PBE) were not significantly altered. Notably, FeNO and nNO went in opposite directions in terms of reduction and increase respectively (Table S2; Figure S2). Following the washout period at week 24, significant changes ($p < .001$) were noted in the quality of life and symptoms scores compared to week 12 values. Similar significant trends occurred after washout for FeNO, nNO, FEV1, and PEF.

The results of the present study showed clinically relevant improvements in upper and lower airway outcomes in relation to quality of life, symptoms and airflow obstruction in response to 12 weeks of dupilumab in patients with T2H UAD. Notably in the upper airway this was accompanied by objective improvements in endoscopic NP score and nNO, the latter reflecting ostiomeatal complex patency allowing nNO to be flushed into the nasal cavity.

TABLE 1 Quality of life, symptom scores, airflow obstruction and endoscopy.

	Baseline (Post run-in)	Week 12 (Post Dupi)	Mean diff (95%CI)	Week 24 (Washout)	Mean diff (95% CI)
SNOT-22	59 (48,70)	16 (9, 24)	43 (29, 57) ***	48 (35, 61)	41 (27, 55) ***
Mini-AQLQ	3.72 (3.24, 4.20)	6.08 (5.60, 6.55)	2.36 (1.77, 2.94) ***	4.82 (4.18, 5.45)	1.49 (0.81, 2.17)***
Nasal Global VAS	7.83 (6.83, 8.84)	2.52 (1.34, 3.71)	5.31 (3.73, 6.88) ***	7.01 (5.66, 8.35)	4.85 (3.02, 6.68)***
Hyposmia VAS	7.70 (6.36, 9.05)	2.35 (1.39, 3.32)	5.35 (3.25 7.46) ***	8.36 (7.36, 9.37)	6.26 (4.67, 7.85)***
TNSS	6.90 (5.63, 8.18)	2.48 (1.45, 3.50)	4.43 (2.64, 6.21) ***	6.37 (4.79, 7.94)	4.11 (2.18, 6.03)***
ACQ-6	2.66 (2.24, 3.07)	0.86 (0.43, 1.29)	1.8 (1.29, 2.31) ***	2.08 (1.55, 2.61)	1.43 (0.84, 2.02)***
PNIF	95 (75, 115)	139 (110, 167)	44 (23, 65) ***	126 (95, 156)	15 (−10, 41)
PEF	413 (362, 464)	473 (409, 538)	60 (30, 90) ***	450 (369, 531)	24 (1, 46)*
FEV_1%	80 (74, 87)	94 (85, 102)	13 (6, 20)***	88 (79, 97)	5 (−1, 12)
Total nasal polyp score	4.33 (3.43, 5.24)	2.14 (1.39, 2.89)	2.19 (1.72, 2.66) ***		

Abbreviations: SNOT-22, 22-item sinonasal outcome test; mini-AQLQ, mini asthma quality of life questionnaire; nasal global VAS, nasal global visual analogue scale; hyposmia VAS, hyposmia visual analogue scale; TNSS, total nasal symptom score; ACQ-6, 6-item asthma control questionnaire; PNIF, peak nasal inspiratory flow; PEF, peak expiratory flow.

Note: Mean (95% CI) values are shown at baseline (following run-in), week 12 (2 weeks following the final dose of dupilumab) and week 24 (14 weeks following the final dose of dupilumab). Mean (95% CI) differences are shown for baseline vs. week 12, and week 24 vs. week 12. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

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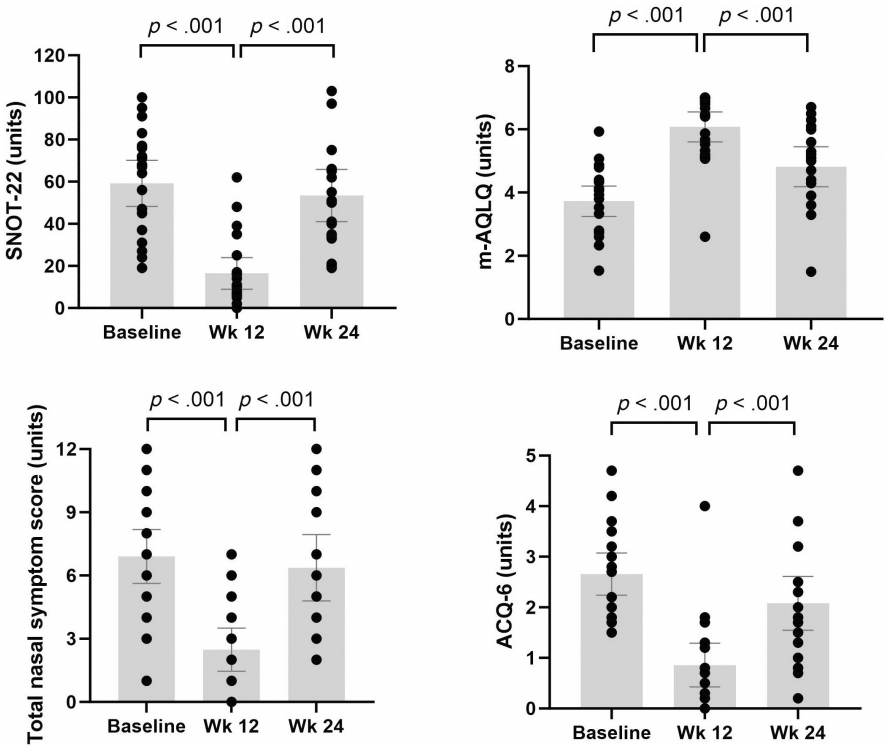

FIGURE 1 Individual and mean (95% CI) values for upper and lower airway quality of life and symptom scores after 12 weeks of dupilumab and after subsequent washout at week 24.

We found a mean change in SNOT-22 score of 43 from a baseline of 59 and in nasal polyp score of 2.19 from a baseline of 4.33. In Sinus-24/52, dupilumab 300 mg 2-weekly produced mean reductions in SNOT-22 scores of 21 and 17 at week 24 from a pooled baseline of 51, along with changes in nasal polyp score of 1.9 and 1.8 from a pooled baseline of 6.0.[5] Here we also reported a mean change of AQLQ of 2.36 from a baseline of 3.72, as compared to LIBERTY QUEST[6] where there was a change of 0.15 after 24 weeks from a baseline of 4.28 also with 300 mg of dupilumab.

We appreciate that our study was relatively small, open-label and had no placebo arm which could impact interpretation of the results. However, participants were followed for an additional 12-week washout, where the quality of life and symptom scores all showed commensurate deterioration comparing values at weeks 12 and 24 trending back towards the baseline values. A placebo arm was not enlisted because dupilumab is available to obtain for severe asthma freely through the national health service (NHS) and therefore as well as potentially affecting recruitment, it was also considered unethical. In conclusion dupilumab treatment in T2H UAD produced clinically relevant improvements in upper and lower airway outcomes in terms of QOL burden, symptom scores and airflow obstruction, in association with reduced NP size and ameliorated OMC patency. Such improvements tended to worsen after a 12 week washout period.

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CONFLICT OF INTEREST STATEMENT

Ms Stewart reports no conflicts of interest. Dr Kuo reports personal fees from AstraZeneca, personal fees from Chiesi, and non-financial support from GSK outside the submitted work. Dr Chan reports personal fees (talks) and support attending ERS from AstraZeneca, personal fees (consulting) from Vitalograph, and personal fees (talks) from Thorasys. Dr Lipworth reports grants, personal fees (consulting, talks and advisory board), other support (attending ATS and ERS) from AstraZeneca; grants, personal fees (talks) and other support (attending ATS, ERS and BTS) from Sanofi and Regeneron, personal fees (talks and advisory board) from Niox; 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 Chiesi; personal fees (consulting and talks) from Lupin, personal fees (consulting and talks) from Glenmark; personal fees (consulting) from Sandoz; grants, personal fees (consulting, talks, advisory board), other support (attending BTS) from Boehringer Ingelheim; and the son of BJL is presently an employee of AstraZeneca.

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DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

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

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Indirect case-matched comparison of anti-IL4Rα versus anti-IL5Rα on airway hyperresponsiveness

To the Editor,

The efficacy of biologics on airway hyperresponsiveness (AHR) has been studied before, but evidence is lacking in regard to which biologic is most effective.[1]

Therefore, we performed a post-hoc case-matched analysis of two prospective single-arm open-label phase IV clinical trials investigating benralizumab (EudraCT2019-003763-22) and dupilumab (EudraCT2021-005593-25) on mannitol induced AHR in patients with uncontrolled type 2 high severe asthma. Twelve out of 21 patients from each study ($n = 24$ total) were case matched according to baseline PD_{10} for appropriate comparison.

Patients taking benralizumab received a higher daily dose of inhaled corticosteroids but exhibited similar asthma control and lung function (Table 1). Dupilumab conferred greater improvements than benralizumab for mannitol PD_{10} as geometric mean fold change (95% CI) from baseline: Dupi 3.77(2.30,6.18) $p < .001$ versus Benra 1.81(1.09,3.01) $p < .05$, amounting to a between treatment doubling difference (95% CI) of 1.06(0.09,2.02) $p < .05$ (Figure 1A). There was also greater attenuation for mannitol response dose ratio (RDR) as geometric mean fold change: Dupi 6.11(2.98,12.50) $p < .001$ versus Benra 1.77(1.00,3.15) $p = .05$ amounting to a between-treatment doubling difference 1.78(0.54,3.03) $p < .01$. Between baseline and week 12, there were no changes in fixed-dose ICS/LABA for patients taking benralizumab. In the same timeframe, the mean daily dose of extra fine BDP/FF 100/6 μg Nexthaler was reduced by 1.2 actuations using the dose counter, equating to a mean 240 μg budesonide equivalent reduction.

After 12 weeks the absolute geometric mean PD_{10} was higher with Dupi 542 mg (437,672) versus Benra 267 mg (158,449) amounting to a geometric mean fold (95%CI) difference 2.08(1.07,4.05)

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