Real-life small airway outcomes in severe asthma patients receiving biologic therapies

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Title: Real life small airway outcomes in severe asthma patients receiving biologic therapies

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Dr. Chan has no relevant conflicts of interest.

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Abbreviations

ACQ	asthma control questionnaire
AX	area under reactance curve
FEF_{25-75}	forced expiratory flow between 25 and 75% of forced vital capacity
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GINA	Global Initiative for Asthma
MCID	minimal clinically important difference
NHS	National Health Service
IgE	immunoglobulin type E
IOS	impulse oscillometry
OCS	oral corticosteroid
PBE	peripheral blood eosinophils
R5	resistance at 5 Hz
R5-R20	difference between resistance at 5 and 20 Hz
R20	resistance at 20 Hz
SAD	small airways dysfunction
SEM	standard error of means
T2	type 2 inflammation

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Clinical implications

FEF_{25-75} should be incorporated to assess improvement in small airways dysfunction (SAD) for severe asthma patients receiving biologics. Impulse oscillometry (IOS) can be useful as an adjunct, particularly in those with baseline IOS-defined SAD.

In Scotland, the current licensed biologic therapies for severe refractory asthma include omalizumab, mepolizumab and benralizumab. These agents have been shown to significantly reduce asthma exacerbations and oral corticosteroid (OCS) use.(1) Although the improvements observed in patient reported outcomes and lung function measured by forced expiratory volume in 1 second (FEV_1) were statistically significant, neither achieved the minimal clinically important difference (MCID).(1)

Small airways dysfunction (SAD) can be measured using spirometry expressed as the forced expiratory flow between 25 and 75% of forced vital capacity (FEF_{25-75}) and using impulse oscillometry (IOS) as the difference between resistance at 5 and 20 Hz (R5-R20).(2, 3) R5-R20 is related to GINA asthma severity,(4) and the use of reliever therapy and long-term OCS is significantly higher in asthmatic patients with abnormal R5-R20 but preserved FEV_1.(5)

As SAD is directly related to asthma severity and type 2 inflammation,(6) we performed a real-life retrospective cohort study to evaluate whether biologic therapies improved SAD in adult patients with severe refractory asthma treated in the National Health Service (NHS) Tayside specialist respiratory clinic. We primarily examined the differences in spirometry (FEV_1% and FEF_{25-75}%), IOS (R5-R20), peripheral blood eosinophils (PBE), asthma control questionnaire (ACQ) and OCS-requiring exacerbations pre- and post-biologic therapy.

56 severe refractory asthma patients who had previously been treated with or were presently receiving biologic therapy with omalizumab, mepolizumab or benralizumab in accordance with national guidelines were included. Pre- and post-biologic data on ACQ, OCS-requiring exacerbations, spirometry, IOS, and PBE were collected. Spirometry (Micromedical, Chatham, UK) and IOS

(Masterscreen^{TM} IOS, Jaeger Ltd) measurements were performed in triplicate according to the European Respiratory Society guidelines with IOS always performed first.

Data were first analysed for normality. Paired Student's T-tests with alpha error set at 0.05 (2-tailed) were applied to compare outcomes pre- and post- biologic therapy. Caldicott Guardian approval was obtained prior to data collection. Values are given as means and SEM.

The mean baseline demographic data, prior to initiation of biologic therapy, were as follows: age 54 years; 14% with aspirin exacerbated respiratory disease; 21% with nasal polyps; ACQ 3.3; FEV_1 81%; FEF_{25-75} 43%; R5 0.50 kPa/L/s; R5-R20 0.12 kPa/L/s; AX 1.14 kPa/L; PBE 572 cells/µL and total IgE 347 kU/L. The mean daily beclomethasone diproprionate equivalent dose of inhaled corticosteroid was 1,889µg; 93% were taking LABA; 61% LAMA; 77% LTRA; 32% theophylline; and 55% oral antihistamine. 34% of patients were taking maintenance OCS prior to biologic initiation. 30% were ex-smokers with the remainder having never smoked. 20, 30 and 6 patients were treated with omalizumab, mepolizumab and benralizumab respectively with the mean duration of therapy between pre- and post-biologic lung function measurements being 10 months. All patients underwent spirometry with 23/56 (41%) also undergoing IOS. 17 patients from the IOS subgroup received anti-IL5 therapy with the remaining receiving omalizumab.

In the overall group (Table 1), FEF_{25-75}% but not FEV_1% improved significantly pre- vs post-biologic therapy. There were also significant improvements in ACQ, OCS-requiring exacerbations and PBE count.

In the SAD subgroup defined by R5-R20≥0.08 kPa/L/s (n=15) (Figure 1), R5-R20 [0.17(0.02) vs 0.11(0.02)] but not AX improved significantly pre- vs post-biologic therapy. Of these, 11 patients received anti-IL5 therapy with the remaining receiving omalizumab. Differences in ACQ [3.7(0.3) vs 1.2(0.3)], OCS-requiring exacerbations [3.8(0.2) vs 0.5(0.2)] and PBE [798(129) vs 122(35)] were also significant in this subgroup. In patients with pre-biologic FEF_{25-75}<60% (n=43), there were significant improvements in ACQ: 3.1(0.3) vs 1.7(0.3); OCS-requiring exacerbations: 4.4(0.3) vs 0.6(0.1); and PBE:

575(65) vs 168(27) cells/μL, but no differences were observed in FEV_1 or IOS. Notably, 10 patients with R5-R20≥0.08kPa/L/s also had a pre-biologic FEF_{25-75}<60%.

When comparing patients according to biologic therapy received (Table 1), FEF_{25-75}% increased significantly in the omalizumab subgroup (15/20 patients) but not in the anti-IL5 (mepolizumab and benralizumab) subgroup (21/36 patients). In both the omalizumab and anti-IL5 subgroups, ACQ and OCS-requiring exacerbations significantly decreased; however, PBE count only decreased significantly in the anti-IL5 subgroup. In the omalizumab subgroup, there were insufficient evaluable data to perform a meaningful analysis of IOS. Although ACQ and PBE improved significantly in patients who were taking maintenance OCS (n=19) at baseline, there were no significant differences observed in spirometry pre- vs post-biologic therapy.

Our study has demonstrated that severe refractory asthma patients with relatively well-preserved baseline FEV_1% experienced significant improvements in small airways function measured by FEF_{25-75}%. This was accompanied by improvements in asthma control, exacerbation frequency and PBE in line with previous studies. FEV_1% improved numerically but was not statistically significant. As expected in the anti-IL5 subgroup, there was a significant reduction in PBE counts which was not seen in the anti-IgE subgroup. ACQ improvements exceeded MCID of 0.5(7) in all groups. Our study observed that in patients with IOS defined SAD (R5-R20≥0.08kPa/L/s)(4) R5-R20 but not R5, R20 or FEF_{25-75} improved significantly with biologic therapy, in conjunction with ACQ, exacerbation frequency and PBE count (Figure 1).

Interestingly, a recent observational study demonstrated that oscillometry parameters improve earlier than spirometry after benralizumab therapy in severe asthma patients.(8) Although the change in R5 (total airway resistance) was significant after 4 weeks of benralizumab, R5-R20 (reflecting peripheral airway resistance)(3) was not statistically altered. Another observational study also showed that biologic therapy responders, defined using a composite of reduction in OCS-requiring exacerbations and asthma symptoms, had significantly higher R5-R20 at baseline compared to partial

or non-responders.(9) As small airway function is directly related to GINA asthma severity(4), this could theoretically propose an argument that FEF_{25-75} and R5-R20 are perhaps the missing link between asthma control, exacerbations and T2 biomarkers. We therefore hypothesise that incorporating IOS into the standard severe asthma workup prior to initiation of biologic therapy may help identify patients most likely to benefit.

The real-life observational aspect of this study was one of its main strengths. However, we recognise the limitations of our retrospective analysis. Firstly, our data was obtained from a single Scottish centre which limits the generalisability of the results. Secondly, our patient numbers are relatively small especially in relation to IOS results and therefore a larger prospective study is required to further validate our results.

In summary our findings have shown that biologic therapies result not only in improvements in asthma control and OCS exacerbation frequency but also in spirometry small airway function. Furthermore, in a subgroup of such patients the presence of abnormal peripheral airway resistance (R5-R20) on IOS was associated with a clinical response to biologic therapy.

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Table 1

	Overall (n = 56)		Anti-IL5 (n = 36)		Omalizumab (n = 20)	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
FEV_1%	81 (3)	85 (3)	81 (3)	87 (3)	80 (6)	81 (6)
FEF_{25-75}%	43 (3)	49 (4)*	46 (4)	52 (5)	37 (5)	44 (7)*
FVC%	100 (3)	104 (3)	100 (3)	104 (3)	101 (5)	103 (5)
FEV_1/FVC ratio	67 (2)	68 (2)	69 (2)	71 (2)	63 (3)	64 (3)
R5 (kPa/L/s)	0.50 (0.03)	0.48 (0.03)	0.46 (0.03)	0.48 (0.04)		
R5 – R20 (kPa/L/s)	0.12 (0.02)	0.12 (0.02)	0.10 (0.02)	0.11 (0.02)		
AX (kPa/L)	1.14 (0.24)	1.30 (0.25)	0.87 (0.17)	1.39 (0.32)		
PBE (cells/µL)	572 (55)	152 (22)***	728 (69)	71 (10)***	309 (53)	288 (41)
OCS exacerbations	4 (0.3)	1 (0.1)***	4 (0.2)	0.5 (0.1)***	4.7 (0.7)	0.6 (0.2)***
ACQ	3.3 (0.23)	1.6 (0.21)***	3.2 (0.3)	1.5 (0.3)***	3.7 (0.3)	1.8 (0.3)***

Table 1 Legend

Comparisons in spirometry, IOS, ACQ, OCS-requiring exacerbations and PBE count pre- and post-biologic therapy. Data presented as means (SEM). ACQ = 6-point asthma control questionnaire score; AX = area under reactance curve; FEV_1 = forced expiratory volume in 1 second; FEF_{25-75} = forced expiratory flow between 25 and 75% of forced vital capacity (FVC); OCS = oral corticosteroid; PBE = peripheral blood eosinophils; R5 = resistance at 5 Hz; R5-R20 = difference between resistance at 5Hz and 20Hz; * denotes $p<0.05$ and ***$p<0.001$

Figure 1 Legend

Values shown as means and standard error of means for significant comparisons in the small airways dysfunction (R5-R20 ≥0.08 kPa/L/s) subgroup according to (a) R5-R20 (b) peripheral blood eosinophil count (c) ACQ and (d) OCS exacerbations pre- and post-biologic therapy.