Impact of nasal polyps on endotype and phenotype in patients with moderate to severe asthma

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INTRODUCTION

Severe refractory type 2 (T2) asthma presents a significant challenge to physicians due to disease heterogeneity, heavy symptom burden, high healthcare consumption costs and concomitant T2 comorbidities.(1) Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common comorbidity directly related to asthma severity,(2) with an approximate prevalence of 30% amongst severe refractory asthmatics.(3) Both conditions are thought to follow the common pathophysiological mechanism of T2 inflammation, typically characterised by increased cytokine expression of IL4, IL5 and IL13 in response to various triggers.(4)

Recently, clinicians have used T2 biomarkers such as peripheral blood eosinophils (PBE), fractional exhaled nitric oxide (FeNO) and allergic status (specific and total IgE) to classify severe asthma patients according to their underlying inflammatory endotype.(1) Eosinophilic proliferation, maturation, survival, activation and migration is governed by IL5, whilst IL13 is associated with FeNO as well as eosinophil tissue migration.(1)

The mainstay therapy for both CRSwNP and asthma consists of inflammatory suppression with local corticosteroids, followed by short courses of systemic corticosteroids for exacerbations.(2) CRSwNP patients refractory to medical therapy have traditionally been referred for consideration of functional endoscopic sinus surgery.(5) Promising results have been reported with anti-IgE, anti-IL5 and anti-IL4rα, proposed to target ‘treatable traits’ according to presence of T2 biomarkers in CRSwNP and asthma.(2) Although all three classes of biologics have resulted in significant improvements in key CRSwNP outcomes (NCT03085797) at the standard licensed subcutaneous doses used in concomitant asthma,(6, 7) an indirect treatment comparison of omalizumab versus dupilumab in CRSwNP has demonstrated significantly greater improvements with the latter.(8) Notably, omalizumab and dupilumab are entering into mainstay therapy for the treatment of nasal polyps in the US,

having been approved by the Food and Drug Administration. Nonetheless, further research is required to determine the impact of endotype on patient response to biologics with regard to NP.

In a recent study of severe asthma patients, PBE >420 cells/μl and FeNO ≥39ppb were found to be the best predictors of concomitant NP.(9) Furthermore, patients with allergic asthma and concomitant allergic rhinitis (AR) exhibit higher levels of PBE and FeNO whilst having lower FEV_1% and FEF_{25-75}% compared to those with allergic asthma alone.(10) Although one study demonstrated that non-asthmatic patients with CRSwNP may have evidence of small airways dysfunction (SAD) measured by spirometry,(11) to our knowledge no studies have been performed to evaluate SAD with spirometry or impulse oscillometry (IOS) in asthma patients with CRSwNP. In contrast to spirometry, IOS involves a tidal breathing manoeuvre used to measure small airways function by assessing peripheral airway resistance as difference in resistance between 5 and 20 Hz (R5-R20), peripheral airway reactance as area under reactance curve (AX) and reactance at 5 Hz (X5), and resonance frequency (fres).

Therefore, we performed a retrospective analysis to identify putative differences in T2 biomarkers, lung function and asthma control in asthma patients with nasal polyps (AwNP) compared to those with asthma alone (A).

METHODS

Database

140 consecutive moderate to severe asthma patients with or without endoscopic NP taking a daily beclomethasone diproprionate (BDP) equivalent inhaled corticosteroid (ICS) dose ≥800μg and at least one second line controller (LABA, LAMA, LTRA or theophylline) were identified from our National Health Service (NHS) specialist respiratory and rhinology clinics over a period of 3 years. CRS patients without endoscopic NP were excluded. Data on PBE,

FeNO, allergic status, spirometry, IOS, asthma control questionnaire (ACQ), oral corticosteroid (OCS) requiring asthma exacerbations, nasal polyp score (NPS) and LM score were retrospectively collected. Values for all T2 biomarkers and lung function were taken prior to initiation of any biologics as these can affect PBE, FeNO and IgE. Values for PBE were taken as the mean of values over the previous year.

FeNO was measured using NIOX VERO (Circassia, Oxford, UK) according to manufacturer's instructions and ATS/ERS guidelines.(12) Blood testing was performed to detect presence of circulating levels of specific IgE antibodies to defined common allergens [Fluorescence enzyme linked immunoassay (Phadia Immunocap 250)]. In our NHS laboratory a specific IgE concentration greater than 0.35 kUA/L is considered a positive result. We characterised specific allergy for each patient either as: (a) number of positive specific IgE responses to aeroallergens including cat, dog, silver birch, house dust mite and grass, and (b) mean specific IgE calculated as the sum of specific IgE in kUA/L divided by the number of aeroallergens tested.

Spirometry (Micromedical, Chatham, UK) was performed according to American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines.(13) Prior to attending the laboratory for spirometry, patients had been asked not to use their short acting beta-2 agonists for 6 hours, long acting beta-2 agonists and muscarinic antagonists, theophyllines and leukotriene receptor antagonists for 48 hours. IOS (Masterscreen, Carefusion Hoechberg, Germany) measurements were performed in triplicate according to the European Respiratory Society guidelines(14) with IOS always performed prior to spirometry. Accuracy of resistance measurements was confirmed on each day with a 3L calibration syringe and a standard 0.2 kPa/L/s resistance mesh. Nasal endoscopy (30° oblique rigid Hopkins 3.0 mm) was performed in our rhinology mega-clinic to obtain NPS with a maximum score of 8. Lund Mackay scores were calculated from the most recent CT scan to radiologically assess CRSwNP burden with a

maximum score of 24. Patients with aspirin exacerbated respiratory disease (AERD) were identified through history.

Statistical Analysis

Data were first analysed for normality using Boxplots. FeNO and specific IgE (kUA/L) values were logarithmically transformed prior to analysis to normalise their distribution. Receiver operating characteristic curves were plotted to determine pre-test probability of NP based on FeNO values. Independent Student's T-tests with alpha error set at 0.05 (2-tailed) were applied. Values are presented as arithmetic means (SEM) and geometric means (SEM) for FeNO and specific IgE.

Ethics

Caldicott Guardian approval was obtained to allow access to any NHS patient identifiable data including allergy, PBE, FeNO, spirometry, IOS, ACQ, asthma exacerbations, NPS and LM score.

RESULTS

Table 1 depicts demographic data showing patients in the AwNP group were more likely to be male and older than those in the A group. 29/78 (37%) and 5/62 (8%) were taking maintenance OCS in the A and AwNP groups respectively. A subgroup of 63/140 (45%) also had measurement of IOS. 27 (A, n=22; AwNP, n=5) and 55 (A, n=37; AwNP, n=18) patients subsequently commenced biologic treatment for asthma with either anti-IgE or anti-IL5 therapy respectively.

In the overall analysis (Table 1), PBE and FeNO were significantly higher whilst total and specific IgE were significantly lower in the AwNP group (Figure 1). Receiver operating characteristic (ROC) curves demonstrated that FeNO ≥22ppb had sensitivity and specificity

values of 81% and 67% respectively for the association of NP (AUC=0.76, p=0.001) whilst PBE ≥324 cells/µl had sensitivity and specificity values of 80% and 46% respectively (AUC 0.67, p=0.003).

AwNP patients had better asthma control as reflected by fewer exacerbations, a lower ICS dose and less impairment of IOS values (R5, R5-R20, X5 and AX). No significant differences in spirometry values were demonstrated between the two groups. The findings were similar when excluding the presence of allergic rhinitis (20/78) among asthma patients without NP (Table 2) and also among patients (AwNP, n=37; A, n=70) taking at least 1,500µg ICS. However, in the sub-analysis of patients taking at least 1,500µg ICS, no significant differences in total or specific IgE were detected.

No significant differences in T2 biomarkers, lung function or asthma control were demonstrated when comparing AwNP patients with aspirin exacerbated respiratory disease (AERD) (n=25) to AwNP patients without aspirin sensitivity (n=37). However, LM scores were significantly higher in AERD patients: 19(1) vs 15(1); $p<0.01$.

In the AwNP group, patients with a NPS ≥5/8 had significantly higher LM scores than those with NPS<5/8: 18(1) v 14(1); $p<0.05$. The overall mean LM score in the AwNP group was 16(1).

When excluding patients on maintenance OCS, PBE and FeNO values remained significantly higher in the AwNP group: 549(41) vs 393(31) $p<0.01$ for PBE and 44(9) vs 20(9) $p<0.05$ for FeNO.

DISCUSSION

Our patients without NP had worse asthma control in terms of more frequent exacerbations and associated higher ICS dose, which was mirrored by worse IOS but not spirometry. This is likely to reflect worse small airways dysfunction (SAD) defined by raised peripheral airway

resistance (R5-R20) and peripheral airway reactance (AX or X5). Our data also showed that asthma control in more severe asthma patients is more closely related to SAD detected by IOS rather than spirometry, since FEF_{25-75} was not significantly different.(15) Although speculative, the significant differences in IOS measurements between the two groups could hypothetically be explained by the presence of two separate conditions on the same disease spectrum. It could be argued that one condition is characterised by inflammation of the nose, paranasal sinuses and larger airways whilst the other involves more distal portions of the bronchial tree. Further research is required to prove this theory and would provide more support for the incorporation of IOS into the standard work up for severe asthma.

In a recent large prospective study, the ATLANTIS group demonstrated that R5-R20 and AX measurements showed comparable prevalence of SAD in asthma patients at severities of GINA 1-3, a higher prevalence at GINA 4 and the highest prevalence at GINA 5.(16) Furthermore, one study aiming to validate the use of forced oscillation R5-R20 using computational models as a measure of small airway narrowing identified 0.08kPa/L/s as representing severe SAD.(17) However, more work is still required for the standardisation of IOS measurements and the establishment of normal ranges. A previous comparison between two forced oscillation devices, IOS Jaeger Masterscreen and airway oscillometry (AOS) Thorasys Tremoflo, has shown better agreement for small airways resistance rather than reactance, and that AOS may be more sensitive at measuring reactance in patients with airflow obstruction.(18)

The results of the present study also showed that the presence of NP in asthma patients was associated with higher PBE and FeNO, lower total and specific allergy burden, whilst asthma control was better along with less small airways dysfunction. The higher PBE and FeNO in AwNP patients is perhaps expected as one might predict that two concomitant T2 conditions would be associated with a higher T2 burden than one alone.(1) According to ROC analysis, FeNO showed superior ability than PBE in determining the presence of NP in our cohort of

asthma patients. FeNO levels were normal in our asthma patients without NP but previous literature shows that even a modest ICS dose, fluticasone proprionate 100µg/day, can produce a 52% FeNO suppression from baseline in mild to moderate asthma.(19) We took care to document PBE and FeNO values prior to patients commencing biologic therapy to avoid confounding. Average PBE counts over the preceding year were calculated as temporal variability in blood eosinophils is an important consideration.(20) In contrast, total and specific IgE were significantly lower in our patients with NP in line with a previous study.(21) Since dupilumab inhibits signalling of IL4 and IL13 suppressing both IgE and FeNO, this perhaps might in part explain why it is highly effective in treating both asthma and NP.(7)

As PBE count has previously been reported to be associated with worse IOS outcomes(22) we were somewhat surprised to find that IOS measurements were worse in our asthma patients without NP where PBE count was lower. Although ACQ was numerically lower in patients with NP, the difference of 0.6 between groups was not significant, which is somewhat surprising given that ACQ is a strong predictor of exacerbations.(23, 24) As expected, our AwNP patients with AERD exhibited higher LM scores than those without aspirin sensitivity, reflecting a greater degree of underlying sinus inflammation in line with previous literature.(25)

Notably similar trends between groups were still observed when excluding group A patients without allergic rhinitis. We felt this was important to ascertain given patients with asthma and allergic rhinitis have worse lung function and higher T2 biomarkers than patients with asthma alone.(10)

We accept our study has several limitations. Firstly, our study was retrospective and did not look at serial changes over time, including the potential impact of instigating biologic therapy. In a five-year prospective follow-up study of 200 newly diagnosed asthma patients, accelerated decline in FEV_1 was associated with nasal polyps, PBE and FeNO.(26) Moreover, we have

recently shown that biologic therapy improves IOS measurements in severe asthma patients with baseline SAD, where NP prevalence was comparable to previous literature estimates.(27) We do not believe that the limited sample size was relevant here as otherwise we would have missed important differences in outcomes such as asthma exacerbations, ICS dose and IOS. Perhaps a larger sample size might have picked up commensurate differences in ACQ and spirometry, although we feel this is somewhat unlikely given the greater improvements in exacerbations compared to either ACQ or FEV_1 in T2 high asthma patients treated with biologics.(28, 29) There may have been a confounding effect from differences observed in ICS dose since this is known to suppress FeNO and PBE levels.(30) However, in the sub-analysis of patients on ICS ≥1,500μg where no significant ICS dose difference was found, FeNO and PBE were still significantly higher in the AwNP group. Moreover, exclusion of patients on maintenance OCS also resulted in significantly higher PBE and FeNO levels in the AwNP group. Repeat analysis was also performed with the exclusion of current smokers, due to their association with suppressed FeNO, yielding similar results to the original analysis.

The results of our study suggest that it may be worthwhile to consider investigating moderate to severe asthma patients with raised PBE and FeNO levels for sino-nasal disease with nasal endoscopy and CT imaging especially those with impaired sense of smell, as this may have subsequent treatment implications. In conclusion, moderate to severe asthma patients with NP have higher levels of PBE and FeNO but lower total and specific allergy than those without NP. Patients without NP had greater small airways dysfunction in association with worse control. Taken together this reinforces the importance of careful characterisation of endotype and phenotype in patients with moderate to severe asthma.

References

1. Chan R, RuiWen Kuo C, Lipworth B. Pragmatic Clinical Perspective on Biologics for Severe Refractory Type 2 Asthma. J Allergy Clin Immunol Pract. 2020.
2. Fokkens WJ, Lund V, Bachert C, Mullol J, Bjermer L, Bousquet J, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. Allergy. 2019;74(12):2312-9.
3. Maio S, Baldacci S, Bresciani M, Simoni M, Latorre M, Murgia N, et al. RItA: The Italian severe/uncontrolled asthma registry. Allergy. 2018;73(3):683-95.
4. Zhang Y, Derycke L, Holtappels G, Wang XD, Zhang L, Bachert C, et al. Th2 cytokines orchestrate the secretion of MUC5AC and MUC5B in IL-5-positive chronic rhinosinusitis with nasal polyps. Allergy. 2019;74(1):131-40.
5. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;58(Suppl S29):1-464.
6. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. J Allergy Clin Immunol. 2020;146(3):595-605.
7. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. The Lancet. 2019.
8. Peters AT, Han JK, Hellings P, Heffler E, Gevaert P, Bachert C, et al. Indirect Treatment Comparison of Biologics in Chronic Rhinosinusitis with Nasal Polyps. J Allergy Clin Immunol Pract. 2021.
9. Maniscalco M, Calabrese C, D'Amato M, Guida P, Molino A, Aliani M, et al. Association between exhaled nitric oxide and nasal polyposis in severe asthma. Respir Med. 2019;152:20-4.
10. Kuo CR, Chan R, Lipworth B. Does unified allergic airway disease impact on lung function and type 2 biomarkers? Allergy, Asthma & Clinical Immunology. 2019;15(1):75.
11. Du K, Zheng M, Zhao Y, Xu W, Hao Y, Wang Y, et al. Impaired small airway function in non-asthmatic chronic rhinosinusitis with nasal polyps. Clinical & Experimental Allergy. 2020;50(12):1362-71.
12. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med. 2005;171(8):912-30.
13. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.
14. Oostveen E, MacLeod D, Lorino H, Farré R, Hantos Z, Desager K, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J. 2003;22(6):1026-41.
15. Jabbal S, Manoharan A, Lipworth J, Lipworth B. Utility of impulse oscillometry in patients with moderate to severe persistent asthma. J Allergy Clin Immunol. 2016;138(2):601-3.
16. Postma DS, Brightling C, Baldi S, Van den Berge M, Fabbri LM, Gagnatelli A, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. Lancet Respir Med. 2019;7(5):402-16.
17. Foy BH, Soares M, Bordas R, Richardson M, Bell A, Singapuri A, et al. Lung Computational Models and the Role of the Small Airways in Asthma. Am J Respir Crit Care Med. 2019;200(8):982-91.
18. Kuo CR, Jabbal S, Lipworth B. I Say IOS You Say AOS: Comparative Bias in Respiratory Impedance Measurements. Lung. 2019;197(4):473-81.
19. Anderson WJ, Short PM, Williamson PA, Lipworth BJ. Inhaled corticosteroid dose response using domiciliary exhaled nitric oxide in persistent asthma: the FENOtype trial. Chest. 2012;142(6):1553-61.
20. Rakowski E, Zhao S, Liu M, Ahuja S, Durmus N, Grunig G, et al. Variability of blood eosinophils in patients in a clinic for severe asthma. Clin Exp Allergy. 2019;49(2):163-70.

21. Stevens WW, Peters AT, Hirsch AG, Nordberg CM, Schwartz BS, Mercer DG, et al. Clinical Characteristics of Patients with Chronic Rhinosinusitis with Nasal Polyps, Asthma, and Aspirin-Exacerbated Respiratory Disease. J Allergy Clin Immunol Pract. 2017;5(4):1061-70.e3.
22. Kuo CR, Jabbal S, Lipworth B. Is small airways dysfunction related to asthma control and type 2 inflammation? Ann Allergy Asthma Immunol. 2018;121(5):631-2.
23. Meltzer EO, Busse WW, Wenzel SE, Belozeroff V, Weng HH, Feng J, et al. Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. J Allergy Clin Immunol. 2011;127(1):167-72.
24. Bateman ED, Reddel HK, Eriksson G, Peterson S, Ostlund O, Sears MR, et al. Overall asthma control: the relationship between current control and future risk. J Allergy Clin Immunol. 2010;125(3):600-8, 8.e1-8.e6.
25. Laidlaw TM, Mullol J, Fan C, Zhang D, Amin N, Khan A, et al. Dupilumab improves nasal polyp burden and asthma control in patients with CRSwNP and AERD. J Allergy Clin Immunol Pract. 2019;7(7):2462-5.e1.
26. Coumou H, Westerhof GA, de Nijs SB, Zwinderman AH, Bel EH. Predictors of accelerated decline in lung function in adult-onset asthma. Eur Respir J. 2018;51(2).
27. Chan R, RuiWen Kuo C, Lipworth B. Real life small airway outcomes in severe asthma patients receiving biologic therapies. The Journal of Allergy and Clinical Immunology: In Practice.
28. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486-96.
29. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;388(10056):2128-41.
30. Jabbal S, Lipworth BJ. Blood eosinophils: The forgotten man of inhaled steroid dose titration. Clin Exp Allergy. 2018;48(1):93-5.

Table 1

Baseline Demographic Data and Comparisons in Type 2 Biomarkers, Lung Function and Asthma Control

	AwNP (SEM)	A (SEM)
Gender (F/M)	28/34	56/22
Age (yrs)	57(2)	51(2)
BMI (kg/m^2)	29(1)	31(1)
Ex-smokers (%)	37	26
Smokers (%)	3	5
LABA (%)	98	94
LAMA (%)	32	55
LTRA (%)	73	63
THEO (%)	11	36
INS (%)	100	26
INAH (%)	10	4
PBE (cells/µl)	549(41)	380(31) **
FeNO (ppb)	42(8)	15(3) **
Specific IgE (kUA/L)	0.25(0.08)	0.84(0.34) *
No. of positive specific IgE	1(0.2)	1.6(0.2) *
Total IgE (kU/L)	250(28)	440(69) *
FEV_1%	84(3)	79(2)
FEF_{25-75}%	42(4)	46(3)
FVC%	106(3)	99(2)
FEV_1/FVC (%)	64(2)	68(2)
R5 (kPa/L/s)	0.45(0.03)	0.60(0.04) **
R5-R20 (kPa/L/s)	0.10(0.02)	0.18(0.03) *
X5 (kPa/L)	-0.14(0.02)	-0.23(0.03) *
AX (kPa/L)	0.89(0.16)	1.79(0.31) *
F_{res} (Hz)	15.59(1.07)	18.68(1.14)
Asthma exac	2(0.3)	4(0.4) ***
ACQ	2.5(0.3)	3.1(0.2)
ICS dose (µg)	1,546(64)	1,892(44) ***

ACQ = asthma control questionnaire; AR = allergic rhinitis; AX = area under reactance curve; AwNP = asthma with nasal polyps; A = asthma without nasal polyps; BMI = body mass index; exac = OCS requiring exacerbations; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; FEF_{25-75} = forced mid expiratory flow rate between 25 and 75% of forced vital capacity (FVC); F_{res} = resonance frequency; ICS = inhaled corticosteroids; INAH = intranasal antihistamine; INS = intranasal corticosteroid; LABA = long acting beta agonist; LAMA = long acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; PBE = peripheral blood eosinophils; R5 = resistance at 5Hz; R5-R20 = difference in resistance between 5 and 20Hz; THEO = theophylline; X5 = reactance at 5Hz; AwNP vs A p<0.05; p<0.01**; p<0.001***; FeNO and specific IgE are shown as geometric mean and SEM.*

Table 2

Comparisons between groups according to use of high dose ICS and absence of AR in group A

	ICS ≥1,500µg			
	AwNP (SEM)	**A (SEM)**	**AwNP (SEM)**	**A w/o AR (SEM)**
PBE (cells/µl)	541(53)	391(34) *	549(41)	387(34) **
FeNO (ppb)	41(9)	15(3) **	42(8)	16(4) **
Specific IgE (kUA/L)	0.25(0.1)	0.77 (0.34)	0.25(0.08)	1.05(0.48) **
No. of positive specific IgE	1.1(0.2)	1.6(0.2)	1(0.2)	1.7(0.2) *
Total IgE (kU/L)	283(40)	467(76)	250(28)	462(81) *
FEV_1%	82(3)	80(2)	84(3)	81(2)
FEF_{25-75}%	40(4)	46(3)	42(4)	46(4)
FVC%	104(3)	99(2)	106(3)	101(2)
FEV_1/FVC (%)	64(2)	68(2)	64(2)	68(2)
R5 (kPa/L/s)	0.46(0.04)	0.62(0.04) *	0.45(0.03)	0.59(0.05) *
R5-R20 (kPa/L/s)	0.11(0.02)	0.18(0.03)	0.10(0.02)	0.18(0.03) *
X5 (kPa/L)	-0.14(0.03)	-0.24(0.03) *	-0.14(0.02)	-0.22(0.03) *
AX (kPa/L)	0.99(0.19)	1.81(0.30) *	0.89(0.15)	1.81(0.38) *
F_{res} (Hz)	15.81(1.29)	19.26(1.16)	15.59(1.07)	18.53(1.38)
Asthma exac	2.8(0.4)	4(0.3) *	2(0.3)	4(0.4) ***
ACQ	2.7(0.3)	3.2(0.2)	2.5(0.3)	3.1(0.2) *
ICS dose (µg)	1,943(24)	1,997(30)	1,546(64)	1,948(48) ***

Figure 1 Legend

Values shown for asthma patients with or without NP (AwNP vs A), as arithmetic means or geometric (FeNO) and standard error of means, for significant comparisons in overall patient population according to (a) FeNO and PBE count (b) total IgE and number of positive specific IgE and (c) R5-R20 and AX