AUDIT UPDATE

Clinical management and outcome of refractory asthma in the UK from the British Thoracic Society Difficult Asthma Registry

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ABSTRACT
Refractory asthma represents a significant unmet clinical need. Data from a national online registry audited clinical outcome in 349 adults with refractory asthma from four UK specialist centres in the British Thoracic Society Difficult Asthma Network. At follow-up, lung function improved, with a reduction in important healthcare outcomes, specifically hospital admission, unscheduled healthcare visits and rescue courses of oral steroids. The most frequent therapeutic intervention was maintenance oral corticosteroids and most steroid sparing agents (apart from omalizumab) demonstrated minimal steroid sparing benefit. A significant unmet clinical need remains in this group, specifically a requirement for therapies which reduce systemic steroid exposure.

BACKGROUND
We have previously published the clinical features of a well characterised group of patients with refractory asthma from specialist UK centres operating established dedicated multidisciplinary assessment protocols and identified important differences between patient groups in individual centres.[1] Using the national online registry, we have now audited clinical outcome in 349 of the 382 patients in the original cohort (median follow-up 3.1 years, IQR 1.9—5.5).

RESULTS
There were no differences in baseline demographical variables in the follow-up cohort compared with those lost to follow-up (online supplementary appendix 1).

At follow-up, there was a significant improvement in lung function and a reduction in important healthcare outcomes, specifically hospital admission, unscheduled healthcare visits and rescue courses of oral steroids (table 1). These effects were generally consistent across clinical centres though unscheduled visits were significantly increased in Manchester (online supplementary appendix 2), reflecting the delivery of care at this centre where patients with an increase in symptoms are encouraged to attend the hospital centre.

There was no significant change in dose of inhaled steroid or reported reliever medication use but there was a significant increase in the number of patients prescribed maintenance oral steroids (from 146 (42%) to 199 (57%)). Only 25 patients (7%) successfully withdrew oral steroids, whereas 78 (22%) were moved onto maintenance oral steroids. There was no significant difference in the dose of oral steroids from baseline to follow-up (16.2±10.4 mg baseline, 15.3±12.8 follow-up).

Consistent with this widespread use of oral steroids, there was a significant reduction in blood eosinophils and increase in body mass index (BMI) (table 1). There was a non-significant trend for the subjects on oral steroids at follow-up to have a higher BMI compared with those not on oral steroids (subjects not on oral steroids 29.5±7.0, subjects on oral steroids 30.9±6.0, p=0.07). However, BMI also increased in patients not on maintenance steroids at follow-up (baseline BMI 28.3±6.8 vs follow-up BMI 29.2±6.9, p<0.001); in this group median rescue steroid exposure was one course of steroids in the preceding 12 months (IQR 0—3).

While blood eosinophils decreased, exhaled nitric oxide paradoxically increased. Because paired fractional exhaled nitric oxide (FeNO) data were only available in a limited number of patients, we examined paired blood eosinophil counts in this subgroup (n=75). The paradoxical fall in blood eosinophils and rise in FeNO were also apparent in this group (eosinophil count in subjects with paired FeNO measurements — baseline eosinophils $\times 10^9$/litre, median 0.33 (IQR 0.12—0.54) vs follow-up eosinophils, median 0.24 (IQR 0.1—0.4), p=0.001; and baseline FeNO ppb, 47 (IQR 22—69) vs follow-up FeNO, 88 (IQR 76—99), p<0.001).

Steroid sparing strategies (online supplementary appendix 3) and additional therapeutic strategies (online supplementary appendix 4) utilised in this refractory population are shown by centre; therapeutic success was defined by the treating clinician. In general, small numbers of patients were tried on steroid-sparing strategies and few were recorded as clinically beneficial. The use of other interventions was infrequent and variable across clinical centres.

Responders to omalizumab (37 of 59 (63%) based on criteria for the National Health Service Outcomes Drug Reimbursement Scheme, http://guidance.nice.org.uk/TA133/Guidance/doc/English) were more likely to be off oral steroids at clinical follow-up (17 of 37 vs 4 of 22, p=0.031, OR 3.8

Table 1 Lung function and healthcare outcomes for cohort

	Baseline	Follow-up	p Value
Pre-bronchodilator FEV$_1$ % predicted (259)	66.4±23.7	72.7±26.8	<0.001
Pre-bronchodilator FVC % predicted (242)	82.7±20.3	86.5±21.5	0.002
Post-bronchodilator FEV$_1$ % predicted (77)	79.2±21.5	77.6±30.7	0.61
Post-bronchodilator FVC % predicted (72)	90.6±19.8	86.3±25.9	0.08
Rescue oral steroids in previous 12 months (302)	4 (2—6)	2 (0—4)	<0.001
Hospital admissions in previous 12 months (324)	0 (0—2)	0 (0—1)	<0.01
Unscheduled visits in previous 12 months (315)	4 (2—6)	2 (0—6)	<0.05
Inhaled steroid dose, BDP equivalent (327)	2000 (1000—2000)	2000 (1200—2000)	0.80
Average daily SABA use (205)	6 (4—9)	8 (4—10)	0.058
Blood eosinophils (206)	0.33 (0.11—0.60)	0.20 (0.09—0.43)	<0.001
FeNO (112)	40 (18—69)	89 (77—102)	<0.001
Body mass index	29.2±6.5	30.2±6.4	<0.001

Group data (mean±SD or median (IQR)) for all subjects are presented in column 1 followed by data for individual centres. Comparisons were made using paired samples t tests or Wilcoxon signed rank tests; significance was taken as p<0.05.
BDP, beclometasone dipropionate; FeNO, fractional expiratory nitric oxide; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; SABA, short-acting β agonist.

(95% CI 1.0 to 18.2), χ^2). Individual responses also support a steroid-sparing effect—in subjects on maintenance oral steroids pre omalizumab (n=28), 9 withdrew oral steroids completely (baseline dose 20 mg (10—35 mg)), 11 had a steroid dose reduction (baseline dose 20 mg (15—20 mg), follow-up 13 mg (10—15 mg), p=0.003, Wilcoxon signed rank test) and 8 had an increase in dose (10 mg (7—10 mg), follow-up 12.25 (10—15 mg), p=0.027, Wilcoxon signed rank test). Of the other 8 subjects whose condition responded to omalizumab only 1 progressed to oral steroids, whereas of those on omalizumab whose condition did not respond, 18 of 22 were on oral steroids at follow-up (15 mg (10—25 mg)).

Using logistic regression, baseline predictors of maintenance oral steroids at follow-up were maintenance oral steroids at baseline (OR 8.3, 95% CI 4.8 to 14.4), male gender (OR 2.2, 95% CI 1.3 to 3.7), and rescue steroids in the preceding year (OR 2.3, 95% CI 1.1 to 4.9). At follow-up, 84 of 127 men (66%) compared with 115 of 222 women (52%) were on maintenance oral steroids (χ^2, p<0.01).

DISCUSSION

This audit provides the first outcome data on a well characterised cohort of adults with severe refractory asthma. We report significant changes in important healthcare outcomes, particularly reductions in unscheduled visits, hospital admissions and rescue oral steroids, which taken collectively suggests a reduction in severe exacerbations. Improvement was also seen in lung function, but notably daily reliever medication use was not different, suggesting persistent symptomatic morbidity in this group. Because of the precise characterisation of this group, we believe this is due to asthma and not other non-asthma comorbidities.

As this is an observational clinical registry, we cannot exclude the possibility that the improvement in healthcare outcomes simply represents 'regression to the mean', since at the time of referral and initial assessment, patients are likely to be clinically unwell. However, 60—75% of patients in these centres are tertiary referrals and had difficult asthma for prolonged periods prior to assessment, making regression to the mean unlikely to

be the entire explanation for the observed improvement. Even at baseline, in this severe asthmatic population, hospital admission rate was relatively low, but unscheduled healthcare contact and rescue steroid courses were high. With appropriate specialist management, hospital admission rates were further reduced, suggesting the economic cost of refractory asthma is unlikely to be driven by hospital admission.

The commonest therapeutic strategy was initiation of maintenance steroids, which is consistent with the reduction in peripheral blood eosinophils and the reduction in rescue oral steroid courses. The dissociation between FeNO, clinical outcome and blood eosinophilia is consistent with other data, which have shown that FeNO-based strategies have not been able to reduce exacerbation rates.[2] In a recent oral steroid tapering study, which included FeNO as part of the steroid reduction algorithm, weekly Asthma Control Questionnaire and forced expiratory volume in 1 s measurement were the major drivers of steroid reduction, with minimal contribution from daily FeNO.[3] Collectively, these data question whether FeNO is useful in adjusting steroid dose in patients on maintenance or frequent bursts of oral steroids.

The increase in BMI is also consistent with more steroid exposure, but BMI also increased in subjects not on maintenance oral steroids at follow-up. This latter group remained on high-dose inhaled steroids but rescue steroid exposure in the preceding 12 months was relatively low (median 1, IQR 0—3), suggesting that BMI increase is not exclusively related to oral steroid exposure in this population, and reduced exercise capacity due to persistent asthma may be relevant.

The best predictor of being on oral steroids was being on them at referral, which might initially suggest that specialist services have a minimal effect on maintenance steroid exposure in this patient population. However, this cohort of patients had well phenotyped refractory asthma after detailed systematic evaluation and issues such as incorrect diagnosis, comorbidities and non-adherence have been identified and these subjects excluded. One of the major advantages and benefits of a specialist difficult asthma service is ensuring precise patient characterisation and appropriateness of high-dose asthma therapy in subjects with refractory asthma.[4]

It is unclear why a greater proportion of men were more likely to be on oral steroids at follow-up. Cohorts of difficult and refractory asthma typically include more women,[4 5] but these data suggest that the requirement for oral steroids, which might be interpreted as one index of severity, is less common in women. Frequency of rescue steroids is also predictive of progression as this identifies someone with steroid-responsive disease prone to exacerbation despite high-dose inhaled therapy. Steroid-sparing strategies (cyclosporin, methotrexate, azathioprine, mycophenolate) are used variably across centres, with limited clinical success. The low trial rate in some centres reflects the potential side effects of these agents, but additionally our observational data also suggest that the success rate of the most commonly used agents (methotrexate and cyclosporin) is low, which is consistent with the conclusions of recent Cochrane reviews of both methotrexate and cyclosporin.[6 7]

The only additional therapeutic intervention that demonstrated a steroid-sparing effect was omalizumab. In subjects who received a clinical trial of omalizumab, the overall response rate was 63% and 20 (71%) of the 28 on oral steroids either withdrew or significantly reduced their oral steroid dose.

In summary, this audit demonstrates improved outcomes with reduced exacerbation rates and healthcare utilisation, but at the cost of increased numbers of subjects on systemic steroids.

Steroid-sparing therapies are infrequently used and are only modestly successful in routine clinical practice. In patients who respond to omalizumab, there is the suggestion of a significant steroid-sparing effect in some but not all subjects. There remains a significant unmet clinical need in this group and specifically a requirement for therapies which reduce systemic steroid exposure.

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Supplementary Appendix 1

Baseline characteristics of cohort with follow-up data; patient demographic data, healthcare utilisation and medication – group data (mean ± SD or median [inter-quartile range]) for all subjects is presented in column 1 followed by data for individual Centres. All patients satisfied the American Thoracic Society definition of refractory asthma (Proceedings of the ATS workshop on refractory asthma:current understanding, recommendations and unanswered questions. American Thoracic Society. Am J Respir Crit Care Med 2000 Dec:162(6):2341-2351). Comparisons were made using one-way analysis of variance or a Kruskal-Wallis analysis of variance of ranks - significance was taken as $p<0.05$

	All **(349)**	**Belfast** **(89)**	**Brompton** **(92)**	**Leicester** **(73)**	**Manchester** **(95)**	
Female (%)	222 (64)	55 (62)	59 (64)	41 (56)	67 (71)	P=0.28
Race White (%)	315 (90.3)	89 (100)	75 (81.5)	60 (82.2)	91 (95.8)	P<0.001
Age (y) First Assessed at Difficult Asthma Service	44.8 ± 13.6	43.2 ± 14.2	43.0 ± 12.6	45.2 ± 13.2	47.7 ± 13.9	P=0.07
Age (y) asthma diagnosed	16 [3 – 35]	20 [2 – 38]	10 [2 -27]	24 [5 – 42]	18 [5 – 33]	P=0.04
Height (m)	1.66 ± 0.10	1.65 ± 0.08	1.68 ± 0.10	1.66 ± 0.11	1.65 ± 0.09	P=0.08
Weight (kg)	81.5 ± 20.0	81.1 ± 19.5	84.8 ± 18.4	82.4 ± 23.6	78.0 ± 18.7	P=0.13
BMI (kg/m^2)	29.1 ± 6.4	29.3 ± 6.3	29.6 ± 6.0	29.7 ± 7.1	28.1 ± 6.2	P=0.32
Smoking status **Never (%)**	210 (60.2)	55(61.8)	63(68.5)	45 (61.6)	47 (49.5)	P=0.13
Ex-smoker (%) **(years since stopped)**	108 (30.9) (9.4 ± 8.0)	26 (29.2) (10.3 ± 9.0)	24 (26.1) (10.6 ± 7.2)	23 (31.5) (11.0 ± 8.1)	35 (36.8) (6.2 ± 6.8)	
Current smoker (%) **(pack years)**	19 (5.4) (14.6 ± 14.9)	6 (6.7) (23.9 ± 24.8)	2 (2.2) (10.2 ± 8.4)	5 (6.8) (11.9 ± 10.2)	6 (6.3) (13.8 ± 11.0)	
Unknown	12 (3.4)	2 (2.2)	3 (3.3)	0	7 (7.4)	
Unscheduled visits in preceding 12 months (n)	4 [2 – 6] (339)	5 [2 – 9] (86)	4 [1.5 – 6] (89)	4 [2 – 6] (73)	3 [2 – 5] (91)	P=0.01
Rescue Steroid Courses	4 [2 – 6]	4 [1 – 6]	5 [2 – 7.5]	5 [2.5 – 6]	2 [0 – 4]	P<0.001

In The Previous Year (n)	(322)	(78)	(81)	(73)	(90)	
Hospital admissions in preceding 12 months (n)	0 [0 – 2] (344)	0 [0 – 1] (87)	1 [0 – 3] (92)	0 [0 – 1] (73)	0 [0 – 1] (92)	P<0.001
Total number of ITU admission (n)	0 [0 – 0] (345)	0 [0 – 0] (87)	0[0 – 1] (92)	0 [0 – 0] (73)	0[0 – 0] (93)	P=0.004
Maintenance Oral Steroids (%)	143 / 348 (41%)	32 / 89 (36%)	51 / 91 (56%)	28 / 73 (38%)	32 / 95 (34%)	P=0.008
Oral Steroid Dose (mg) (n)	15 [10 – 20] (140)	15 [6 – 20] (31)	19 [10 – 20] (52)	10 [8 – 15] (28)	15 [10 – 30] (29)	P=0.06
BDP Equivalent Dose (ug) (n)	2000 [1000 – 2000] (333)	1600 [1000 – 2000] (87)	2000 [2000 – 2000] (88)	2000 [1600 – 2000] (73)	1200 [1000 – 2000] (85)	P<0.001
SABA use per day	6 [4 – 8] (238)	8 [4 – 9] (29)	6 [4 – 8] (68)	4 [2 – 9] (57)	8 [5.25 – 10] (84)	P=0.003
LABA use(%)	324/330 (98%)	87/88 (99%)	89/90 (99%)	66/70 (94%)	82/82 (100%)	P=0.047
Theophylline n (%)	132 / 345 (38%)	36 / 89 (40%)	48 / 90 (53%)	24 / 73 (33%)	24 / 93 (26%)	P=0.001
Nebuliser Use (%)	149 / 344 (43%)	42 / 88 (48%)	58 / 90 (64%)	18 / 73 (25%)	31 / 93 (33%)	P<0.001
Any Steroid Sparing Medications	4 / 344 (1%)	1 / 86 (1%)	0 / 89 (0%)	1 / 73 (1%)	2 / 90 (2%)	P=0.514
Anti-IgE Treatment n (%)	3 / 346 (1%)	0 (0%)	0 (0%)	0 (0%)	3 (3%)	P=0.044
PPI (%)	99 / 346 (29%)	25 / 89 (28%)	30 / 90 (33%)	17 / 73 (23%)	27 / 94 (29%)	P=0.571
Aspirin / NSAID Sensitivity n (%)	32/334 (10%)	7/87 (8%)	6/85 (7%)	9/70 (13%)	10/92 (11%)	P=0.59
Anti-histamine n (%)	80/342 (23%)	15/88 (17%)	24/89 (27%)	14/72 (19%)	27/93 (29%)	P=0.18
Nasal Steroids n (%)	84/342 (25%)	26/88 (30%)	21/89 (24%)	13/72 (18%)	24/93 (26%)	P=0.40
Leukotriene Receptor Antagonists n (%)	125/343 (36%)	48/88 (55%)	38/89 (43%)	21/73 (29%)	18//93 (19%)	P<0.001

Pre-bronchodilator spirometry (n)	(338)	(89)	(89)	(71)	(89)	
FEV$_1$ (L)	1.95 ± 0.82	1.94 ± 0.70	1.85 ± .079	2.20 ± 0.87	1.86 ± 0.90	P=0.03
% predicted	66.0 ± 23.7	66.8 ± 23.9	59.9 ± 20.6	74.1 ± 22.8	65.5 ± 25.7	P=0.004
FVC (L)	3.09 ± 1.04	3.08 ± 0.89	3.25 ± 1.09	3.13 ± 1.12	2.91 ± 1.05	P=0.19
% predicted	82.1 ± 20.0	82.9 ± 20.1	83.0 ± 18.3	82.6 ± 21.6	79.9 ± 20.5	P=0.70
FEV1 / FVC ratio %	63.0 ± 15.1	63.4 ± 14.9	55.7 ± 14.5	70.6 ± 13.2	63.5 ± 14.4	P<0.001
Subjects with baseline post-bronchodilator study (n)	(239)	(57)	(44)	(69)	(69)	
PreBronchodilatorFEV$_1$ (L)	1.91 ± 0.84	1.69 ± 0.63	1.83 ± 0.81	2.20 ± 0.87	1.84 ± 0.91	P=0.004
(% predicted)	(64.3± 23.2)	(58.0 ± 18.6)	(58.8 ± 20.9)	(74.1 ± 23.1)	(64.0 ± 25.3)	P<0.001
Pre-Bronchodilator FVC (L)	3.07 ± 1.09	2.99 ± 0.96	3.34 ± 1.18	3.13 ± 1.13	2.92 ± 1.08	P=0.24
(% predicted)	(81.1 ± 20.2)	(80.1 ± 19.5)	(83.9 ± 18.5)	(82.8 ± 21.9)	(79.0± 20.4)	P=0.57
Post-bronchodilator FEV$_1$ (L)	2.19 ± 0.89	1.94 ± 0.68	2.29 ± 1.04	2.37 ± 0.87	2.15 ± 0.91	P=0.04
(% predicted)	(74.1 ± 24.0)	(66.7 ± 20.9)	(74.1 ± 26.6)	(80.0± 22.8)	(75.1 ± 24.7)	P=0.03
Post-Bronchodilator FVC (L)	3.32 ± 1.09	3.21 ± 0.93	3.64 ± 1.29	3.30 ± 1.13	3.24 ± 1.02	
(% predicted)	(88.1± 19.2)	(86.5 ± 18.8)	(91.2 ± 21.3)	(87.7 ± 20.8)	(87.8 ± 17.0)	P=0.22
						P=0.70
Post-bronchodilator FEV$_1$/FVC ratio (%)	65.6 ± 14.3	61.1 ± 12.6	61.6 ± 15.6	71.7 ± 12.1	65.4 ± 14.9	
						P<0.001

Supplementary appendix 2- Lung function and healthcare outcomes of cohort with follow-up data by Clinical Centre – group data (mean ± SD or median [inter-quartile range]) for all subjects is presented in column 1 followed by data for individual Centres. Comparisons were made using paired analysis (paired t-test or Wilcoxon test as appropriate) - significance was taken as P<0.05.

	All (349)	Belfast (89)	Brompton (92)	Leicester (73)	Manchester (95)	
Pre-bronchodilator FEV1 %predicted (n)	72.7 ± 27.7 (273)	81.8 ± 22.5 (83)	62.8 ± 23.5 (67)	76.1 ± 25.5 (70)	66.4 ± 36.6 (53)	P<0.001
FVC % predicted(n)	86.3 ± 21.6 (263)	95 ± 18.5 (83)	78.7 ± 20.8 (66)	83.2 ± 22 (69)	85.9 ± 22.8 (45)	P<0.001
Post bronchodilator FEV1 % predicted (n)	73.8 ± 32.5 (110)	88.8 ± 38.5 (6)	57.8 ± 39.7 (23)	79.4 ± 26.7 (69)	65.1 ± 35.8 (12)	P<0.05
Post bronchodilator FVC %predicted (n)	83.8± 26.6 (101)	80.5 ± 42.1 (6)	81.4 ± 26.7 (17)	83 ± 26.3 (68)	95.3 ± 16.3 (10)	P=0.543
Unscheduled visits in preceding 12 months (n)	2 [0 − 6] (324)	1 [0 − 3] (86)	1 [0–4.25] (86)	0 [0 − 1] (70)	10 [6 − 13] (82)	P<0.001
Rescue Steroid Courses in the preceding 12 months (n)	2[0 - 4] (326)	2 [0 − 4] (85)	2 [1 − 5] (88)	2 [1 − 4] (71)	2 [0 − 4] (82)	P=0.507
Hospital admissions in preceding 12	0 [0 − 1]	0 [0 − 1]	0 [0 − 1.5]	0 [0 − 0]	0 [0 − 1]	P<0.01

months (n)	(329)	(87)	(89)	(71)	(82)	
BDP Equivalent Dose, ug (n)	2000 [1000-2000] (341)	1600 [800 – 2000] (88)	2000 [2000 -2000] (90)	1600 [1600 – 2000] (69)	2000 [1000 – 2000] (94)	P<0.001
SABA use per day	7 [4 – 10] (242)	7[4 – 9] (21)	4 [2 – 8] (71)	6 [2 – 10] (59)	8 [6 – 10] (91)	P<0.001

Supplementary Appendix 3

Steroid sparing strategies by Centre – the denominator for steroid sparing strategies is 224 (patients who were on maintenance oral steroids either at baseline or follow-up).

	All **(n=224)**	**Belfast** **(n= 55)**	**Brompton** **(n=67)**	**Leicester** **(n=47)**	**Manchester** **(n=55)**	
Methotrexate **Tried** **Success**	47 (31%) 12 (26%)	8 (15%) 0 (0%)	3 (5%) 2 (67%)	22 (47) 4 (18%)	14 (25%) 6 (43%)	P<0.001
Cyclosporin **Tried** **Success**	23 (10%) 7 (30%)	9 (14%) 3 (33%)	7 (10%) 2 (29%)	2 (4%) 0 (0%)	5 (9%) 2 (40%)	P=0.27
Mycophenolate **Tried** **Success**	3 (1%) 2 (67%)	2 (4%) 2 (100%)	0 (0%) -	0 (0%) -	1 (2%) 0 (0%)	-
Azathioprine **Tried** **Success**	11 (5%) 3 (27%)	1 (2%) 0 (0%)	2 (3%) 1 (50%)	3 (6%) 2 (67%)	5 (9%) 0 (0%)	P=0.27
Any steroid sparing strategy Tried	64 (29%)	15 (27%)	10 (15%)	23 (49%)	16 (29%)	P=0.001

Supplementary Appendix 4

Additional therapeutic options by centre- the denominator for other strategies is 349 (all subjects).

	All (n=349)	Belfast (n= 89)	Brompton (n=92)	Leicester (n=73)	Manchester (n=95)	
Itraconazole						
Tried	18 (5%)	1 (1%)	1 (1%)	2 (3%)	14 (15%)	P<0.001
Success	14 (78%)	0 (0%)	0 (0%)	1 (50%)	12 (86%)	
Subcutaneous Bricanyl						
Tried	15 (4%)	1 (1%)	12 (13%)	0 (0%)	2 (2%)	P<0.001
Success	6 (40%)	1 (100%)	5 (42%)	-	0 (0%)	
IVAminophylline						
Tried	28 (8%)	1 (1%)	21 (23%)	1 (1%)	5 (5%)	P<0.001
Success	22 (79%)	0 (0%)	16 (76%)	1 (100%)	5 (100%)	
SMART						
Tried	85 (24%)	21 (24%)	3 (3%)	15 (21%)	46 (48%)	P<0.001
Success	75 (88%)	18 (86%)	3 (100%)	8 (53%)	44 (96%)	
Omalizumab						
Tried	59 (17%)	12 (13%)	35 (38%)	1 (1%)	11 (12%)	P<0.001
Success	37 (63%)	7 (58%)	23 (66%)	0 (0%)	7 (64%)	