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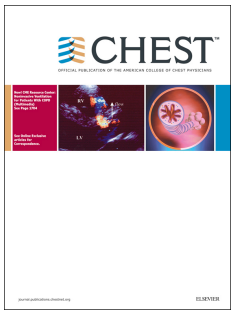

Omalizumab Treatment Response in a Severe Allergic Asthma Population with Overlapping COPD

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Abstract

Background

Asthma and chronic obstructive pulmonary disease (COPD) are common airway diseases. Individuals with overlapping asthma and COPD experience increased health impairment and severe disease exacerbations. Efficacious treatment options are required for this population. Omalizumab (anti-IgE) therapy is effective in patients with severe, persistent asthma, but limited data are available on efficacy in populations with overlapping asthma and COPD.

Methods

Data from the Australian Xolair Registry (AXR) was used to compare treatment responses in individuals with asthma-COPD overlap to severe asthma alone. Participants were assessed at baseline and after 6 months of omalizumab treatment. We utilised several different definitions of asthma-COPD overlap. First we compared participants with a previous doctor diagnosis of COPD to participants with no COPD diagnosis. We then made comparisons based on baseline lung function, comparing participants with post-bronchodilator FEV_1 <80% predicted to >80% predicted. In the FEV_1<80% population, analysis was further stratified based on smoking history.

Results

Omalizumab treatment markedly improved asthma control and health related quality of life in all populations assessed, based on ACQ-5 and AQLQ questionnaire scores. Omalizumab treatment did not improve lung function

(FEV_1, FVC or FEV_1/FVC ratio) in populations that were enriched for asthma-COPD overlap (diagnosis of COPD or FEV_1<80%/ever smokers).

Conclusions

Our study suggests that omalizumab improves asthma control and health related quality of life in individuals with severe allergic asthma and overlapping COPD. These findings provide real-world efficacy data for this patient population and suggest omalizumab is useful in the management of severe asthma with COPD overlap.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are common obstructive airway diseases [1,2]. These diseases may overlap, resulting in greater health impairment and more frequent and severe exacerbations than observed in individuals with asthma or COPD alone [3-7]. The challenges related to the clinical management of patients with an overlap of asthma and COPD are increasingly recognised, prompting the development of a consensus-based document by the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [8]. Improving outcomes for this population and determining efficacious treatment options are high priorities.

Asthma-COPD overlap is an umbrella term that encompasses several different phenotypes, such as eosinophilic COPD, severe asthma with incomplete airflow reversibility and asthma with smoking. This has prompted calls to further evaluate patients for specific mechanistic pathways (endotypes) and to then target specific treatments for each mechanistic pathway, rather than based on disease label [9].

There are promising new targeted therapies for the treatment of severe treatment-refractory asthma that target the Th2/eosinophilic/allergic pathways in asthma (reviewed in [10]). These pathways can also occur in COPD [11-13], however, a diagnosis of COPD is typically an exclusion criterion for clinical trials in asthma and vice versa [14,15]. As a result, limited clinical data exists on the efficacy of these treatments in a population with overlapping asthma and COPD.

Omalizumab (Xolair) is an effective therapy for patients with severe, persistent asthma [16-33], that acts by binding to serum IgE, reducing mast cell, basophil, dendritic cell and B cell responses [17,34-37]. To date, there is limited data available on the efficacy of omalizumab in populations with overlapping asthma and COPD.

The Australian Xolair Registry (AXR) was established to evaluate the real-world use of omalizumab for treatment-resistant severe allergic asthma in Australia [38]. This registry captured a significant proportion of all Australians prescribed omalizumab (n=177) and provides the opportunity to assess treatment response in patients with overlapping COPD. Analysis of the AXR population provides unbiased and structured insight into the real-world patient population receiving treatment.

The aim of this study was to determine the efficacy of omalizumab treatment in individuals with severe allergic asthma and overlapping COPD. Further, we aimed to compare treatment response in participants with asthma-COPD overlap to participants with severe allergic asthma alone. We hypothesised that response to omalizumab treatment would be similar in both populations.

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Materials & Methods

Study Design

The Australasian Xolair Registry (AXR) is an investigator-initiated and led multi-centre, non-interventional, observational study that recruited patients with severe allergic asthma who were being assessed for eligibility and commencement of government-subsidised omalizumab through the Australian Pharmaceutical Benefits Scheme (PBS) [38,39]. Participants with severe allergic asthma were enrolled between October 2011 and June 30, 2014 and assessments performed at baseline and after 6 months of omalizumab treatment. In order to be eligible for subsidised omalizumab via the Australian PBS, and thus part of the registry, participants needed to demonstrate that they had severe uncontrolled allergic asthma despite high dose inhaled corticosteroids (ICS) and long-acting beta agonists (LABA), with optimal inhaler technique and adherence. This was determined using the following criteria: a confirmed diagnosis of asthma, under the care of a respiratory physician or allergist for at least 12 months, a duration of asthma for at least 1 year, an FEV1 less than 80%, an ACQ5 ≥ 2 and treatment with 1000mcg fluticasone propionate equivalent and at least salmeterol 50mcg bd or eformoterol 12 mcg bd. Prior use of oral corticosteroids was also required. Inhaler technique and adherence were assessed and deemed optimal by the prescribing physicians.

The study was approved by the Hunter New England Human Research Ethics Committee (HNEHREC Ref: 11/10/19/5.03). Participants provided written, informed consent upon entry into the data registry.

Assessments

Data were collected prospectively at enrolment and at 6 months after initiating omalizumab therapy, as previously described [38]. The baseline demographic and clinical variables collected included age, gender, duration of allergic asthma, comorbid disease profile (including atopy, rhinitis, eczema and anaphylaxis), asthma therapy and asthma control. Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio were also collected, where possible pre and post bronchodilator (BD). Asthma control and health status was recorded using the 5-item Asthma Control Questionnaire (ACQ-5) [40] and Asthma Quality of Life Questionnaire (AQLQ) [41].

Asthma-COPD Overlap Definitions

We assessed the response to omalizumab treatment in an asthma-COPD overlap population, utilising several different definitions that have been reported in the literature. A total of 177 participants in the AXR cohort had baseline and 6-month follow-up data available for assessment. All participants were prescribed high dose ICS and LABAs. We performed two primary comparisons of this dataset. In analysis one, we compared participants with a previous doctor diagnosis of COPD (n=17) to a population with no COPD diagnosis (n=160). Analysis two involved a subpopulation of the AXR registry with post-bronchodilator (BD) spirometry data available at baseline (n=72). Individuals with post-BD FEV_1 >80% predicted (n=17) were compared to those with an FEV_1 <80% (n=55). We further stratified the FEV1 <80% group based on available

smoking history (n=47), and compared never smokers (n=36) to ever smokers (n=11).

Statistical Analysis

Statistical analysis was performed using STATA 13 (StataCorp, College Station, TX, USA). Baseline features for analyses one and two were performed, using Chi-squared or Fisher's exact test for categorical data and Student's t test or Wilcoxon rank sum test for continuous data as appropriate. Further comparison of baseline features for analysis two were performed using one-way ANOVA or Kruskall Wallis test as appropriate, with Bonferroni correction for multiple comparisons. Paired analyses were conducted on baseline and follow-up clinical, quality of life and medication data to determine response to omalizumab treatment, using McNemar's Chi-squared or exact test for categorical or Wilcoxon sign rank test for continuous data. A p-value <0.05 was considered significant.

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Results

Omalizumab in Doctor Diagnosed COPD

A higher prevalence of previous smoking history was observed in the population with severe allergic asthma and concomitant doctor-diagnosed COPD (66.7% versus 25.3%, p=0.002). Participants with doctor-diagnosed COPD were older (62.3 versus 50.3 years of age, p=0.002) and had higher rates of eczema (29.4% versus 10.6%, p=0.026), but there were no further differences in the baseline characteristics (Table 1).

Asthma control and health related quality of life (HRQoL) significantly improved in those with severe allergic asthma and doctor diagnosed COPD (ACQ-5 at baseline improved from 3.68 to 1.69 post-omalizumab treatment, p<0.0001; AQLQ improved from 4.03 to 5.56, p<0.016) (Figure 1A/B, e-1). A similar degree of improvement was observed in participants without doctor-diagnosed COPD (ACQ-5 from 3.49 to 1.99, p<0.0001; AQLQ from 3.47 to 4.61, p<0.0001) (Figure 1A/B, e-1). Improvements were observed for all domains of the AQLQ in both populations, with the exception of the activity component in the COPD-diagnosed population (Table e-1). All improvements exceeded the MCID (0.5 point improvement) for each assessment.

At 6-month follow-up, improved lung function was observed after omalizumab treatment in the non-COPD diagnosed population, for pre-BD FEV_1 (from 57.6% to 63.1%, p=0.02) and FEV_1/FVC ratio (from 58.5 to 62.1, p=0.009), and post-BD FEV_1/FVC ratio (from 58.0 to 64.3, p=0.0003) (Figure 1C/D, e-1). No

improvement was seen in lung function (pre or post-BD FEV_1, FVC, FEV_1/FVC ratio) in the COPD-diagnosed population.

Omalizumab in COPD Determined by Spirometry

Participants with severe allergic asthma and post-BD FEV_1 >80% predicted and <80% predicted were compared. Notably, all participants with a doctor diagnosis of COPD were in the FEV_1<80% population.

At baseline, participants with severe allergic asthma and post-BD FEV_1<80% population had lower FEV_1 (pre-BD 49.3% versus 84.4%, p<0.0001; post-BD 54.6% versus 93.4%), FVC (pre-BD 73.0 versus 98.1, p<0.0001; post-BD 78.6% versus 105.5%) and FEV_1/FVC ratio (pre-BD 53.5 versus 66.8, p=0.001; post-BD 55.0 versus 69.1) (Table 2), as expected based on the categorisation of participants. The FEV_1<80% group also had a significantly longer duration of asthma (26.4 versus 7.9 years, p=0.046). When compared based on smoking history, never smokers with post-BD FEV_1<80% had lower baseline pre-BD FEV_1, compared to ever smokers (44.7% versus 60.1%) (Table 3). No further differences were observed in medication usage or asthma control and HRQoL scores at baseline for either comparison (Table 2/3).

Again, all populations assessed (regardless of smoking history) had improved asthma control and HRQoL after omalizumab treatment, as measured by the ACQ-5 (Figure 2/3A, e-2/3) and the AQLQ (Figure 2/3B, e-2/3). Improvements in individual domains of the AQLQ questionnaire failed to reach statistical significance the FEV_1>80% population and ever smokers, likely due to limited

availability of AQLQ data in these populations (FEV_1>80% population n=5; ever smoker n=3) (Table e-2/3). Improvements again exceeded the MCID for each assessment and a similar degree of improvement was observed for each population.

At 6-month follow-up, there was no significant improvement in FEV_1, FVC or FEV_1/FVC ratio in the FEV_1>80% population after omalizumab treatment (Figure 2/e-2). In contrast, the FEV_1<80% population had significant improvements in FEV_1 (pre-BD from 47.8% to 56.6%, p=0.006; post-BD from 55.4% to 65.5%, p=0.004) and FEV_1/FVC ratio (pre-BD from 52.9 to 59.2, p=0.002; post-BD from 53.3 to 60.6, p=0.0007), following treatment (Figure 2/e-2). The FEV_1<80% population also had a significant decrease in oral corticosteroid use (from 47.3% to 36.4%, p=0.031; Table e-2). When compared based on smoking history, never smokers had significant improvements in lung function, assessed by FEV_1 (pre-BD from 43.8% to 56.7%, p=0.001; post-BD from 51.9% to 66.1%, p=0.001) and FEV_1/FVC ratio (pre-BD from 51.5 to 59.6, p=0.002; post-BD from 51.9 to 61.1, p=0.001) and pre-BD FVC (from 68.8% to 76.3%, p=0.04)(Figure 3/e-3). No improvements were observed in spirometry results (pre or post-BD FEV_1, FVC, FEV_1/FVC ratio) in the ever smoker population (Table e-3).

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Discussion

This study suggests that omalizumab improves asthma control and health related quality of life in individuals with severe allergic asthma and overlapping COPD. When compared, similar improvements were seen between individuals with overlapping COPD and individuals with severe allergic asthma alone.

Data on the response to omalizumab treatment in asthma-COPD overlap populations is extremely limited. Clinical trials of omalizumab efficacy have typically excluded patients with a doctor diagnosis of COPD, which would have excluded approximately 10% of the AXR population. Our assessment provides insights into real-life evaluation of patients with severe allergic asthma. These are important findings as they contribute new knowledge for managing patients with severe allergic asthma who have an overlapping COPD phenotype; an estimated 20% of the population [4].

Identification of individuals with asthma-COPD overlap can be complex. The GOLD/GINA recommendations for asthma, COPD and asthma-COPD overlap provide some guidance [8]. However, adapting these recommendations to the severe treatment-refractory asthma population reveals the real-world difficulties in determining asthma-COPD overlap status in this patient group. Assessment based on lung function measures, such as post-BD FEV_1/FVC <0.7 or FEV_1 <80% predicted includes a large proportion of the severe asthma population [42,43] and does not provide additional insight into patients with potential asthma-COPD overlap. Evidence of BD-mediated reversibility is also proposed as a diagnostic criterion to differentiate asthma from COPD, but does

not rule out asthma-COPD overlap. Further, reversibility may not be present in severe asthma.

In the AXR population, when assessed based on a pre-existing doctor diagnosis of COPD, only 17/177 participants (9.6%) were classified as having asthma-COPD overlap. This likely underestimates the true population, when compared to published prevalence data [4]. Comparison based on a post-BD FEV_1 <80% included 55/72 participants (76.4%), which likely overestimates the overlap population. Further stratification based on a smoking history resulted in 11/47 participants with previous smoking history (23.4%). Interestingly, participants with a doctor diagnosis of COPD fell within both never smoker and ever smoker categories in our analysis. While none of these approaches can definitively confirm asthma-COPD overlap status, the use of several diagnostic criteria is a strength of this study, since it allows for assessment of omalizumab treatment effects across different populations. Our analyses represent the real-world situation where differentiation between severe asthma, COPD and asthma-COPD overlap is problematic.

Only two publications have previously reported on omalizumab treatment responses in patients with asthma-COPD overlap, with a total of 13 patients [44,45]. An assessment of 59 severe persistent allergic asthma patients treated with omalizumab identified 3 patients with asthma-COPD overlap and reported reduced asthma exacerbations and improved asthma control after treatment for 1 year, although no statistical comparisons were performed [45]. A second study of 10 asthma-COPD overlap patients (definition not provided) found that

omalizumab treatment improved lung function (FEV_1, PEF and FEV_1/FVC) and asthma control [44]. These studies provide support for the efficacy of omalizumab treatment in a small number of patients with both severe asthma and COPD. However, these findings are from a very small number of participants and provide no insight into how responses compare to a matched population of severe asthma patients without overlapping COPD. These comparisons are a further strength of this present study.

Our dataset provides insight into a further 17 patients (based on a doctor diagnosis of COPD), as well as populations further enriched for asthma-COPD overlap based on post-BD FEV_1 (n=55) and smoking history (n=11). Importantly, our findings provide direct comparisons to patients with severe allergic asthma lacking overlapping COPD features. This dataset reflects the realities of the difficulty in diagnosing asthma-COPD overlap in this patient population and highlights beneficial response to treatment regardless of overlapping COPD.

Collectively our analyses provide consistent findings on the response to omalizumab treatment in an asthma-COPD overlap-enriched population. Across all comparison groups, we observed significant improvements in asthma control and quality of life after treatment, regardless of COPD status. For all groups, these improvements exceeded the minimally clinically important difference and a similar degree of improvement was seen in all patient populations. These findings indicate that omalizumab treatment has similar efficacy regardless of diagnostic phenotype.

However, no improvement in lung function was observed in populations enriched for asthma-COPD overlap (doctor diagnosed COPD or ever smokers with post-BD FEV_1<80%). These results are not surprising due to the irreversible nature of COPD and are quite consistent with findings from the omalizumab clinical trials, where asthma control, HRQoL and exacerbation rates are consistently reduced, while improvement in lung function are quite variable [33]. We did observe improvements in lung function in populations not enriched for asthma-COPD overlap (no doctor diagnosed COPD and never smokers with post-BD FEV_1<80%). This finding is consistent with severe real-life effectiveness studies documenting omalizumab response in individuals with asthma [32,46]. Further, other targeted therapies such as the IL-5Rα benralizumab, may improve FEV_1 in individuals with COPD [47].

A growing body of literature has demonstrated a functional role for IgE in some COPD populations [11-13,48-52]. A subset of COPD patients has increased Th2 cytokines and eosinophilic disease and omalizumab treatment may be beneficial in this population. Indeed, monoclonal antibodies against Th2 cytokines are currently being trialled in this population (e.g. mepolizumab (anti-IL-5) in NCT02105961, NCT02105948, NCT01463644).

Whilst these results are informative we acknowledge some limitations. Non-random sampling was used to recruit participants for the registry, no placebo group was available to assess for placebo effects and there are difficulties in defining asthma-COPD overlap. Analysis one was based on a doctor diagnosis of COPD, which does not provide objective confirmation of disease. Objective

documentation of emphysema (e.g high resolution CT or diffusion capacity assessment) in this population could be assessed in future studies. Due to insufficient power we could not assess the potential impact of asthma duration or age on treatment response or possible sub-phenotypes within the population. Further, our analyses still provide relatively small numbers of patients with overlapping asthma-COPD. Further real world studies evaluating the effect of omalizumab in an asthma-COPD overlap population will provide additional insights for treatment.

Conclusion

Omalizumab treatment improves asthma control and quality of life in a severe allergic asthma population, with associated COPD. These findings provide real-world efficacy data for this patient population and suggest omalizumab is useful for management of patients with asthma-COPD overlap.

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Author Contributions

HP had full access to all of the data in the study and takes responsibility for integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. PG is the guarantor of this paper, taking responsibility for the integrity of the work as a whole, from inception to published article. SM, PGG, HP and VMM contributed substantially to the study design, data analysis and interpretation and the writing of the manuscript.

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Figure Legends:

Figure 1: Comparisons Based on Doctor Diagnosis of COPD. A) Asthma control (ACQ-5) and B) health related quality of life (AQLQ) questionnaire scores and C) pre and D) post-BD FEV_1/FVC results, at baseline (open bars) and 6-month follow-up of omalizumab therapy (closed bars). Graphs represent mean ± SD. *p <0.05, ***p<0.001, ****p<0.0001.

Figure 2: Comparisons Based on baseline post-BD FEV_1 Assessment (>80% predicted versus <80%). A) Asthma control (ACQ-5) and B) health related quality of life (AQLQ) questionnaire scores and C) pre and D) post-BD FEV_1/FVC spirometry results, at baseline (open bars) and 6-month follow-up of omalizumab therapy (closed bars). Graphs represent mean ± SD. ***p<0.001, ****p<0.0001.

Figure 3: Comparisons Based on Smoking History (Never versus Ever Smoker) in the post-BD FEV_1 <80% population. A) Asthma control (ACQ-5) and B) health related quality of life (AQLQ) questionnaire scores and C) pre and D) post-BD FEV_1/FVC spirometry results, at baseline (open bars) and 6-month follow-up of omalizumab therapy (closed bars). Graphs represent mean ± SD. *p <0.05, ***p<0.001, ****p<0.0001.

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Table 1: Baseline Participant Characteristics - Doctor Diagnosis of COPD.

	No COPD N=160	COPD N=17	P value
Age α	50.3 (14.9)	62.3 (11.3)	**0.002**
Male¥	66 (41.3%)	4 (23.5%)	0.197
Smoking:¥			**0.002**
Never	92 (74.8%)	5 (33.3%)	
Current	4 (3.3%)	0	
Ex	27 (22.0%)	10 (66. 7%)	
Pack years β	9.0 (1.0, 30.0)	25.0 (9.9, 41.9)	0.242
Weight, kg; β	80.1 (67.0, 96.2)	84.8 (64.0, 91.3)	0.954
BMI β	29.0 (25.1, 34.3)	29.1 (27.4, 35.4)	0.462
IgE β	283.5 (159.0, 624.0)	358.0 (242.0, 797.0)	0.146
Atopy¥	159 (99.4%)	17 (100%)	1.0
Rhinitis¥	80 (50%)	7 (41.2%)	0.489
Eczema¥	17 (10.6%)	5 (29.4%)	**0.026**
Anaphylaxis¥	14 (8.8%)	1 (5.9%)	1.0
Asthma duration, yrs β	20.6 (6.0, 40.0)	6.4 (2.3, 62.4)	0.283
Lung Function			
Pre BD spirometry	N=88	N=10	
FEV1 % predicted (Pre BD) α	57.2 (20.9)	50.5 (12.7)	0.374
FVC % predicted (Pre BD) α	77.7 (19.5)	64.0 (16.8)	0.059
FEV1/FVC (Pre BD) α	57.9 (12.9)	60.7 (11.5)	0.500
Post BD spirometry	N=67	N=6	
FEV1 % predicted (Post BD) α	64.1 (21.5)	60.1 (9.7)	0.660
FVC % predicted (Post BD) α	86.2 (19.4)	71.3 (14.7)	0.073
FEV1/FVC (Post BD) α	57.9 (12.2)	65.8 (7.8)	0.124
Medication Use			
OCS use¥	78 (50.3%)	9 (52.9%)	0.838
OCS dose (mg/day) β range	10 (10, 25), 2-50	10 (7.5, 12.5), 5-15	0.292
ICS dose (BDPmcg/day) β	2000 (1600, 2240)	2000 (1600, 2000)	0.665
Long Acting Muscarinic Antagonist¥	29 (18.2%)	6 (35.3%)	0.094
Leukotriene Modifier¥	16 (10.1%)	1 (5.9%)	1.0
Theophylline¥	6 (3.8%)	1 (5.9%)	0.515
Omalizumab dose	450 (300, 750)	600 (450, 625)	0.282
Asthma Questionnaire Scores			
ACQ-5 score α	3.48 (0.94)	3.68 (1.16)	0.418
AQLQ Scores	N=78	N=8	
AQLQ Activity α	3.75 (1.20)	4.33 (1.38)	0.202
AQLQ Symptoms α	3.46 (1.30)	3.91 (1.56)	0.361
AQLQ Emotions α	3.36 (1.36)	3.58 (1.64)	0.676
AQLQ Environment α	3.81 (1.49)	4.16 (1.81)	0.538
AQLQ Mean Score α	3.59 (1.17)	4.03 (1.45)	0.320

[α] mean (SD), student's t-test; [β] median (Q1,Q2), Wilcoxon rank sum test; [¥] n(%), chi^2 or Fisher's exact test

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Table 2: Baseline Patient Characteristics – Based on Post-BD FEV_1.

	Post β2 FEV1% ≥ 80% N=17	**Post β2 FEV1% < 80% N=55**	**P value**
Age α	49.2 (17.9)	52.9 (13.7)	0.373
Male¥	4 (23.5%)	24 (43.6%)	0.165
Smoking:¥			1.0
Never	14 (82.4%)	36 (76.6%)	
Current	0	2 (4.3%)	
Ex	3 (17.7%)	9 (19.2%)	
Pack years β	1.0 (1.0, 21.0)	9.3 (1.1, 67.5)	0.294
Weight, kg; β	80.0 (67.5, 102.0)	81.0 (73.0, 94.0)	0.905
BMI β	32.0 (24.5, 37.5)	29.6 (25.6, 35.7)	0.685
IgE β	271.0 (150.0, 593.0)	309.0 (174.0, 840.0)	0.320
Atopy¥	17 (100%)	55 (100%)	
Rhinitis¥	11 (64.7%)	26 (47.3%)	0.209
Eczema¥	1 (5.9%)	8 (14.6%)	0.676
Anaphylaxis¥	1 (5.9%)	4 (7.3%)	1.0
Asthma duration, yrs β	7.9 (3.8, 31. 6)	26.4 (8.0, 41.3)	**0.046**
Dr diagnosis COPD¥	0	6/54 (11.1%)	0.324
Lung Function			
Pre BD spirometry	N=17	N=54	
FEV1 % predicted (Pre BD) α	84.4 (16.0)	49.3 (14.3)	**<0.0001**
FVC % predicted (Pre BD) α	98.1 (13.1)	73.0 (16.9)	**<0.0001**
FEV1/FVC (Pre BD) α	66.8 (9.8)	53.5 (11.9)	**0.001**
Post BD spirometry	N=17	N=55	
FEV1 % predicted (Post BD) α	93.4 (10.9)	54.6 (13.0)	**<0.0001**
FVC % predicted (Post BD) α	105.5 (13.6)	78.6 (16.4)	**<0.0001**
FEV1/FVC (Post BD) α	69.1 (7.7)	55.0 (11.2)	**<0.0001**
Medication Use			
OCS use¥	9 (56.3%)	27 (49.1%)	0.614
OCS dose (mg/day) β, range	10 (7.5, 18.8), 2.5-25	10 (8, 25), 2-50	0.887
ICS dose (BDP mcg/day) β	2000 (1440, 3320)	2000 (1600, 2880)	0.699
Long Acting Muscarinic Antagonist¥	4 (23.5%)	12 (21.8%)	1.0
Leukotriene Modifier¥	2 (12.5%)	2 (3.6%)	0.217
Theophylline¥	0	3 (5.5%)	1.0
Omalizumab dose	450 (300, 600)	600 (300, 750)	0.075
Asthma Questionnaire Scores			
ACQ-5 score α	3.30 (0.97)	3.42 (1.02)	0.691
AQLQ Scores	N=8	N=29	
AQLQ Activity α	3.86 (1.43)	3.75 (1.30)	0.826
AQLQ Symptoms α	3.28 (1.64)	3.57 (1.37)	0.614
AQLQ Emotions α	3.20 (1.57)	3.30 (1.21)	0.842
AQLQ Environment α	3.53 (1.54)	3.59 (1.59)	0.920

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AQLQ Mean Score [α]	3.50 (1.47)	3.59 (1.27)	0.859

[α] mean (SD), student's t-test; [β] median (Q1,Q2), Wilcoxon rank sum test; [¥] n(%), chi^2 or Fisher's exact test

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Table 3: Baseline Patient Characteristics, Based on Post-BD FEV_1 and Smoking History.

	Post β2 FEV1% ≥ 80% N=17	Post β2 FEV1% < 80%		P value
		Never smoker N=36	Ever smoker N=11	
Age [α]	49.2 (17.9)	49.8 (14.1)	56. 9 (11.4)	0.334
Male[¥]	4 (23.5%)	18 (50.0%)	3 (27.3%)	0.136
Smoking:[¥]				**<0.0001**
Never	14 (82.4%)	36 (100%)	0	
Current	0	0	2 (18.2%)	
Ex	3 (17.7%)	0	9 (81.8%)	
Pack years [β]	1.0 (1.0, 21.0)	N/A	9.3 (1.1, 67.5)	0.294
Weight, kg; [β]	80.0 (67.5, 102.0)	78.0 (68.8, 94.4)	91.30 (78.0, 97.0)	0.412
BMI [β]	32.0 (24.5, 37.5)	28.9 (24.4, 34.1)	36.4 (27.3, 38.8)	0.172
IgE [β]	271.0 (150.0, 593.0)	285.5 (166.5, 893.5)	578.0 (278.0, 840.0)	0.466
Atopy[¥]	17 (100%)	36 (100%)	11 (100%)	
Rhinitis[¥]	11 (64.7%)	19 (52.8%)	3 (27.3%)	0.162
Eczema[¥]	1 (5.9%)	6 (16.7%)	0	0.337
Anaphylaxis[¥]	1 (5.9%)	4 (11.1%)	0	0.825
Asthma duration, yrs [β]	7.9 (3.8, 31.6)	20.0 (6.7, 37.3)	32.8 (1.7, 38.3)	0.236
Dr Diagnosis COPD[¥]	0	2/35 (5.7%)	2/11 (18.2%)	0.194
Lung Function				
Pre BD spirometry	N=17	N=35	N=11	
FEV1 % predicted (Pre BD) [α]	84.4 (16.0)	44.7 (12.4)[≠]	60.1 (14.6)[≠μ]	**<0.0001**
FVC % predicted (Pre BD) [α]	98.1 (13.4)	68.9 (16.5) [≠]	84.7 (15.5) [μ]	**<0.0001**
FEV1/FVC (Pre BD) [α]	66.8 (9.8)	51.9 (12.4) [≠]	55.2 (9.6) [≠]	**0.0002**
Post BD spirometry	N=17	N=36	N=11	
FEV1 % predicted (Post BD) [α]	93.4 (10.9)	51.9 (12.4) [≠]	60.3 (13.7) [≠]	**<0.0001**

FVC % predicted (Post BD) [α]	105.5 (13.6)	77.5 (17.7) [≠]	84.3 (14.6) [≠]	**<0.0001**
FEV1/FVC (Post BD) [α]	69.1 (7.7)	53.6 (11.7) [≠]	55.7 (8.6) [≠]	**<0.0001**
Medication Use				
OCS use[¥]	9 (56.3%)	16 (44.4%)	7 (63.6%)	0.510
OCS dose (mg/day) [β], range	10 (7.50, 18.75),2.5-25	11.3 (10, 25), 2-50	10 (5, 12.5), 5-25	0.341
ICS dose (BDPmcg/day), [β]	2000 (1440, 3320)	2000 (1600, 2760)	2000 (1600, 3600)	0.869
Long Acting Muscarinic Antagonist[¥]	4 (23.5%)	8 (22.2%)	2 (18.2%)	1.0
Leukotriene Modifier[¥]	2 (12.5%)	1 (2.8%)	1 (9.1%)	0.264
Theophylline[¥]	0	3 (8.3%)	0	0.743
Omalizumab dose	450 (300, 600)	600 (300, 750)	750 (300, 750)	**0.049**
Asthma Questionnaire Scores				
ACQ-5 Score [α]	3.30 (0.97)	3.52 (1.01)	3.73 (0.62)	0.507
AQLQ Scores	N=8	N=25	N=3	
AQLQ Activity [α]	3.86 (1.43)	3.92 (1.27)	2.18 (0.24)	0.094
AQLQ Symptoms [α]	3.28 (1.64)	3.77 (1.37)	2.19 (0.39)	0.170
AQLQ Emotions [α]	3.20 (1.57)	3.47 (1.20)	2.0 (0.53)	0.172
AQLQ Environment [α]	3.53 (1.54)	3.79 (1.59)	1.92 (0.38)	0.152
AQLQ Mean Score [α]	3.50 (1.47)	3.78 (1.25)	2.13 (0.11)	0.115

[α] mean (SD), one-way ANOVA; [β] median (Q1,Q2), Kruskall Wallis test; [¥] n(%),chi2 or Fisher's exact test.

[≠]post hoc sig vs Post β2 FEV1% ≥ 80%; [μ] post hoc sig vs Post β2 FEV1% < 80% & never smoker

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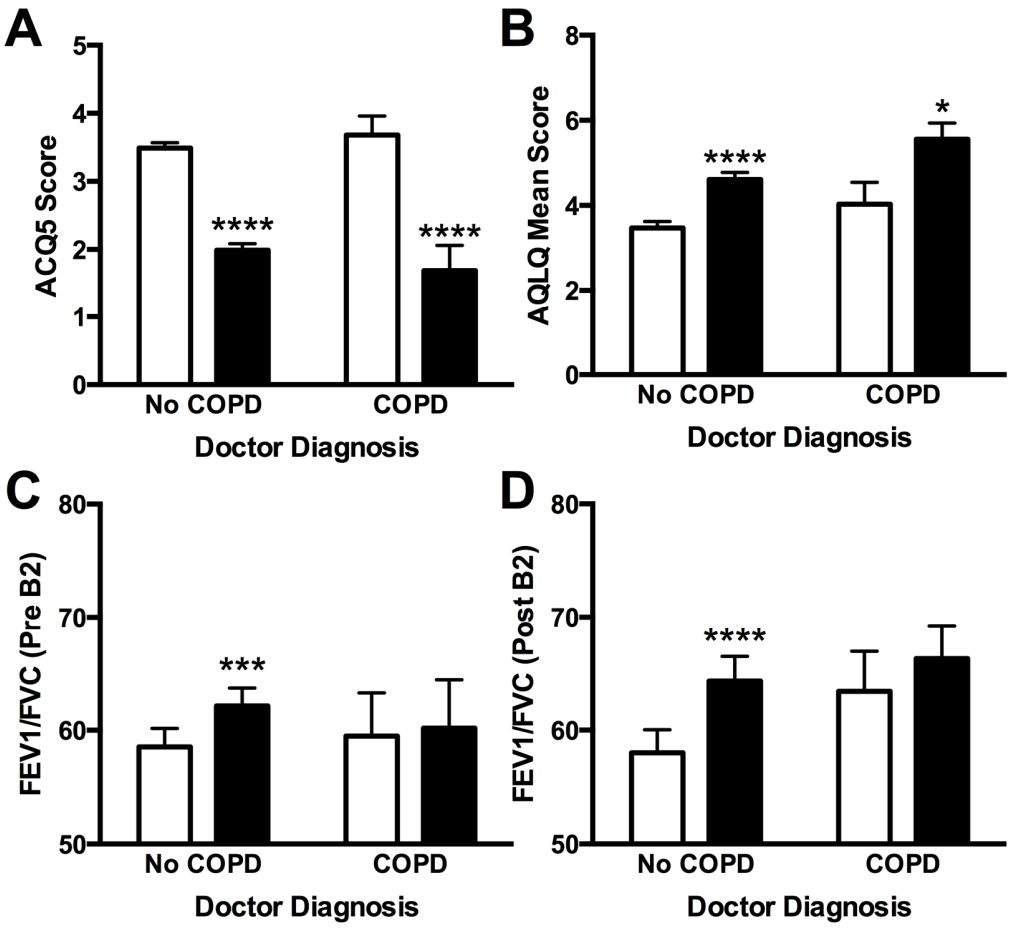
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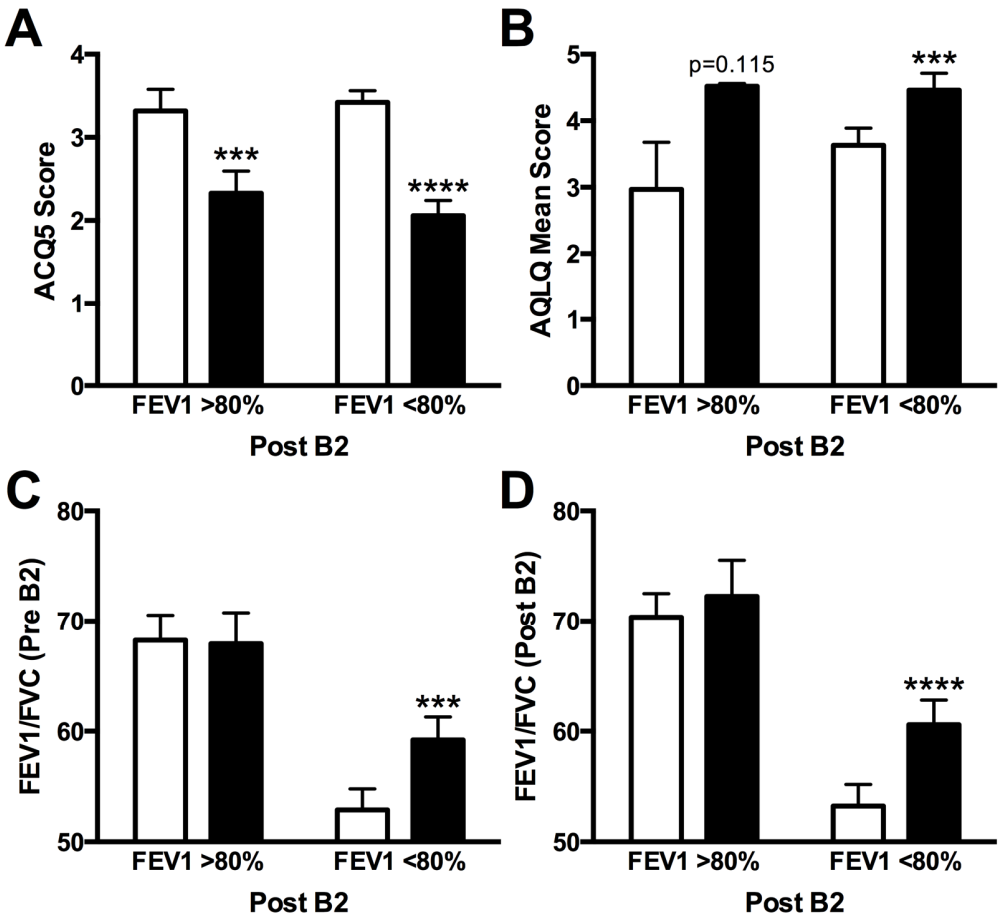
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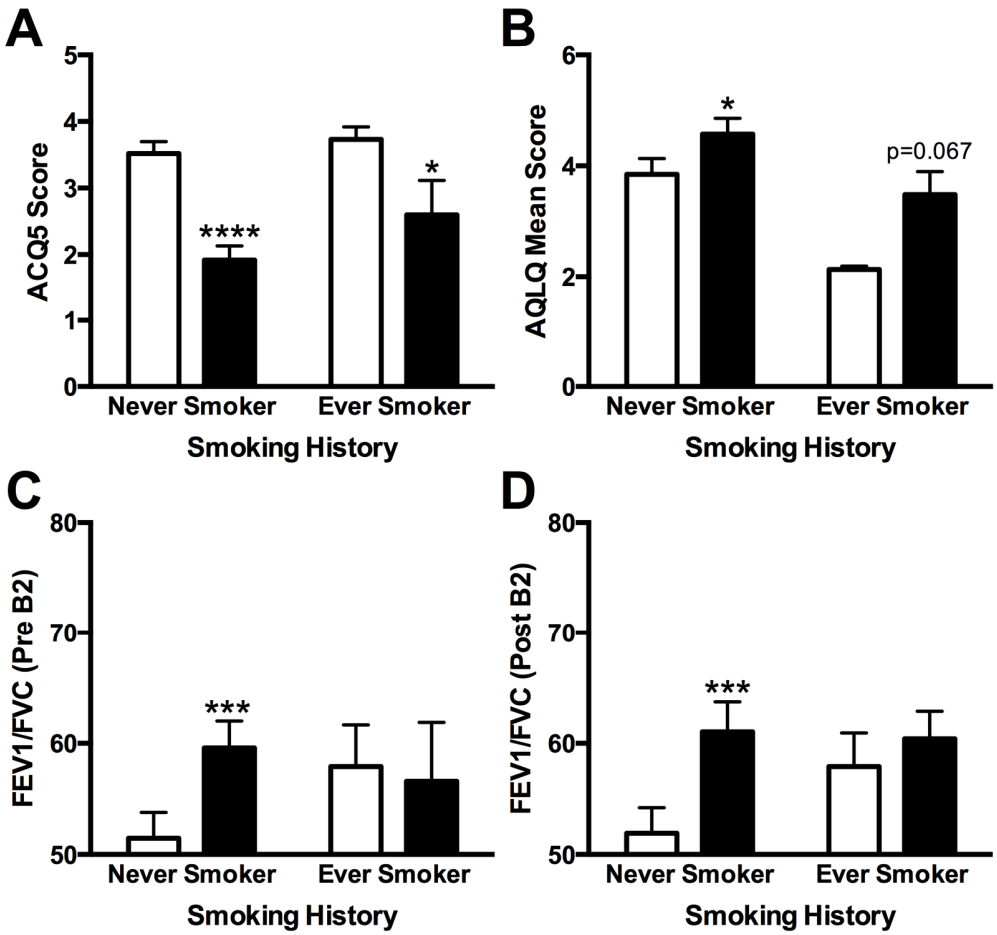
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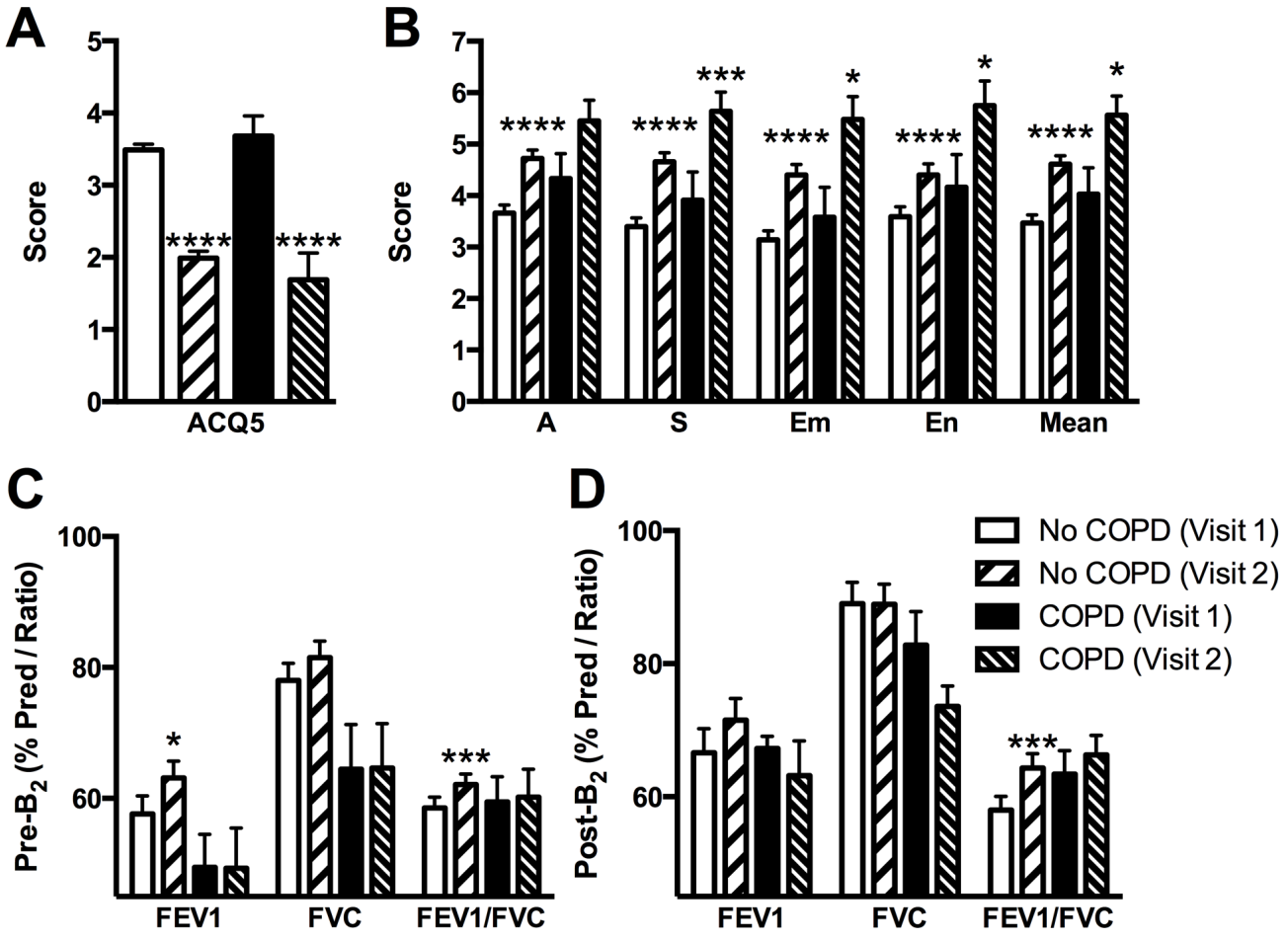

e-Figure 1: Comparisons based on doctor diagnosis of COPD. A) Asthma control (ACQ-5) and B) quality of life (AQLQ) questionnaire scores and C) pre and D) post-BD FEV_1/FVC spirometry results, at baseline (open bars) and 6-month follow-up of omalizumab therapy (closed bars). Graphs represent mean ± SD. *p <0.05, ***p<0.001, ****p<0.0001. A = Activity, S = Symptoms, Em = Emotions, En = Environment.

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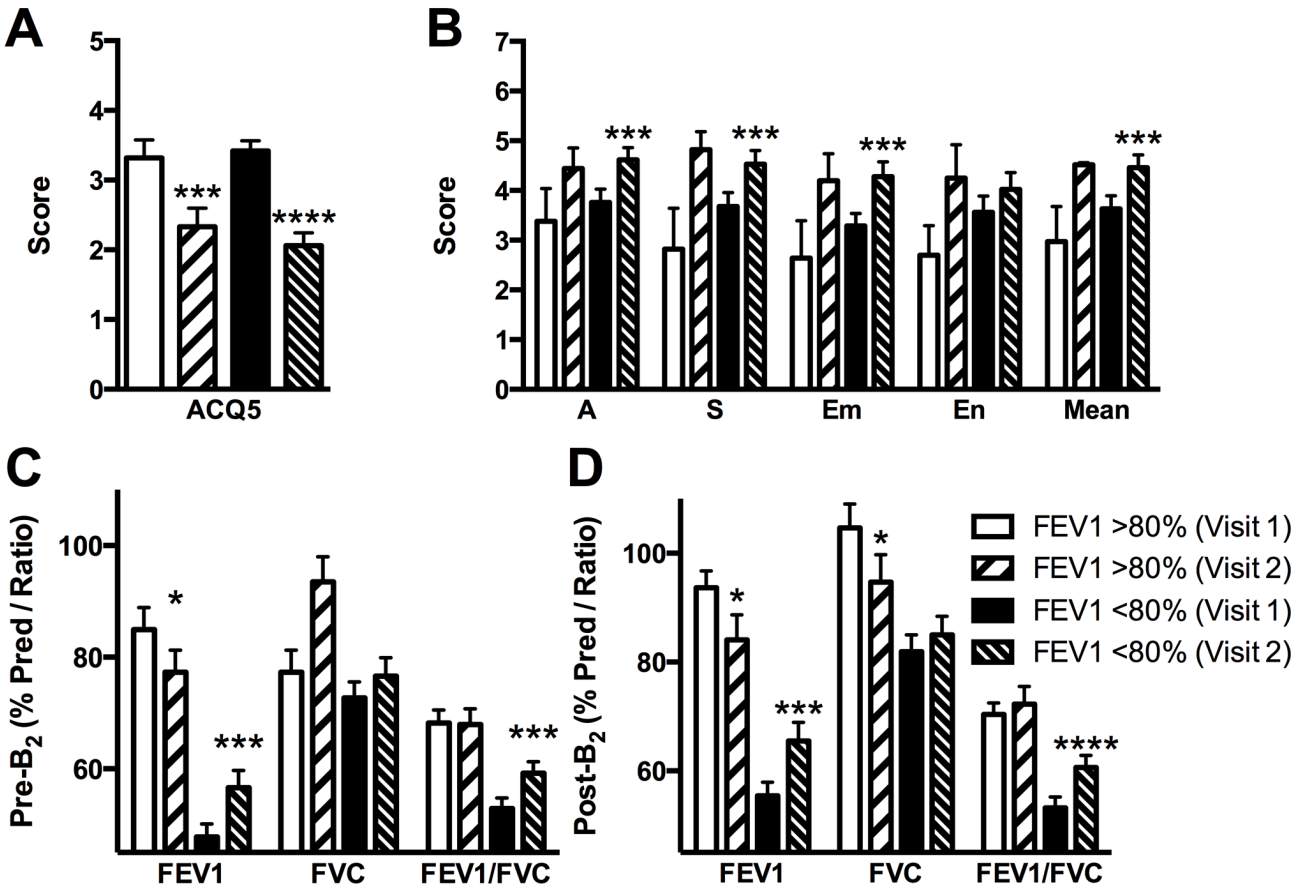

e-Figure 2: Comparisons based on baseline post-BD FEV_1 assessment (>80% predicted versus <80%). A) Asthma control (ACQ-5) and B) quality of life (AQLQ) questionnaire scores and C) pre and D) post-BD FEV_1/FVC spirometry results, at baseline (open bars) and 6-month follow-up of omalizumab therapy (closed bars). Graphs represent mean ± SD. *p <0.05, ***p<0.001, ****p<0.0001. A = Activity, S = Symptoms, Em = Emotions, En = Environment.

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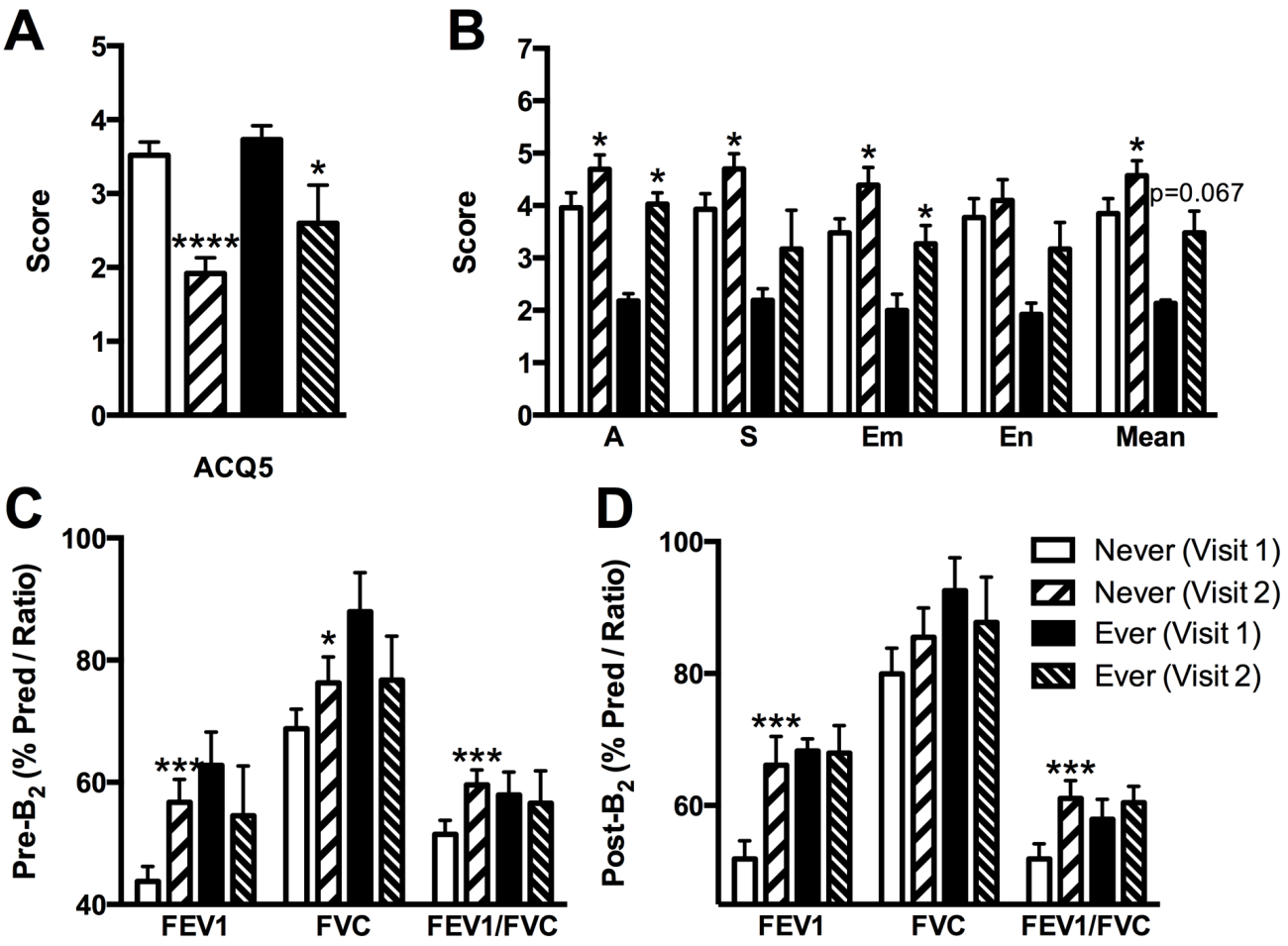

e-Figure 3: Comparisons based on smoking history (never versus ever smoker) in the post-BD FEV_1 <80% population. A) Asthma control (ACQ-5) and B) quality of life (AQLQ) questionnaire scores and C) pre and D) post-BD FEV_1/FVC spirometry results, at baseline (open bars) and 6-month follow-up of omalizumab therapy (closed bars). Graphs represent mean ± SD. *p <0.05, ***p<0.001, ****p<0.0001. A = Activity, S = Symptoms, Em = Emotions, En = Environment.

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e-Table 1: Response to Omalizumab Treatment, Based on Doctor Diagnosis of COPD.

	No COPD N=160				COPD N=17			
	N	Visit1	Visit 2	P value	N	Visit1	Visit 2	P value
Weight, kg; [β]	153	80.10 (67.50, 95.80)	80.0 (68.0, 94.30)	0.116	17	84.80 (64.0, 91.30)	86.80 (69.90, 89.90)	0.449
Lung Function								
FEV1 % predicted (Pre BD) [α]	62	57.62 (21.88)	63.11 (20.27)	**0.020**	7	49.47 (13.28)	49.34 (16.22)	0.981
FVC % predicted (Pre BD) [α]	62	78.01 (20.51)	81.50 (19.86)	0.114	7	64.47 (18.04)	64.66 (17.90)	0.977
FEV1/FVC (Pre BD) [α]	66	58.53 (13.35)	62.13 (12.86)	**0.009**	9	59.48 (11.45)	60.18 (12.81)	0.771
FEV1 % predicted (Post BD) [α]	38	66.59 (22.41)	71.51 (20.09)	0.109	3	67.24 (3.18)	63.18 (9.03)	0.623
FVC % predicted (Post BD) [α]	38	89.02 (19.73)	88.92 (18.70)	0.969	3	82.80 (8.74)	73.60 (5.28)	0.371
FEV1/FVC (Post BD) [α]	40	58.01 (12.83)	64.34 (13.77)	**0.0003**	3	63.41 (6.11)	66.29 (5.09)	0.265
Medication Use								
OCS use[¥]	155	77 (49.68%)	72 (46.45%)	0.251	17	9 (52.94%)	9 (52.94%)	1.0
OCS dose (mg/day) [β]	64	10 (10, 20), 2-50	10 (10, 25), 2-75	0.731	9	10 (7.5, 12.5), 5-15	10 (7.5, 12.5), 5-15	0.317
ICS dose (BDPmcg/day) [β], range	145	2000 (1600, 2240)	2000 (1600, 2780)	0.380	14	2000 (1600, 2000)	2000 (1600, 2000)	
Long Acting Muscarinic Antagonist[¥]	158	29 (18.35%)	36 (22.78%)	**0.016**	17	6 (35.29%)	5 (29.41%)	1.0
Leukotriene Modifier[¥]	157	16 (10.19%)	16 (10.19%)	1.0	17	1 (5.88%)	1 (5.88%)	1.0
Theophylline[¥]	158	6 (3.80%)	6 (3.80%)	1.0	17	1 (5.88%)	1 (5.88%)	1.0
Asthma Questionnaire Scores								
ACQ-5 Score [α]	144	3.49 (0.95)	1.99 (1.15)	**<0.0001**	17	3.68 (1.16)	1.69 (1.53)	**<0.0001**
AQLQ Activity [α]	60	3.66 (1.22)	4.72 (1.27)	**<0.0001**	8	4.33 (1.38)	5.45 (1.15)	0.079
AQLQ Symptoms [α]	60	3.40 (1.31)	4.66 (1.33)	**<0.0001**	8	3.91 (1.56)	5.64 (1.05)	**0.005**
AQLQ Emotions [α]	60	3.14 (1.35)	4.40 (1.58)	**<0.0001**	8	3.58 (1.64)	5.48 (1.25)	**0.025**
AQLQ Environment [α]	60	3.59 (1.48)	4.40 (1.69)	**<0.0001**	8	4.16 (1.81)	5.75 (1.35)	**0.020**
AQLQ Mean Score [A]	60	3.47 (1.20)	4.61 (1.28)	**<0.0001**	8	4.03 (1.45)	5.56 (1.07)	**0.016**

[β] median (Q1,Q2), Wilcoxon sign rank test; [α] mean (SD), paired t-test; [¥] n(%), McNemar's chi^2 or exact test.

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e-Table 2: Response to Omalizumab Treatment, Based on Post-BD FEV_1 Results.

	Post β2 FEV1% ≥ 80% N=17				Post β2 FEV1% < 80% N=55			
	N	Visit1	Visit 2	P value	N	Visit1	Visit 2	P value
Weight, kg; [β]	17	80.0 (67.50, 102.0)	78.60 (67.50, 100.0)	0.740	55	81.0 (73.0, 94.0)	83.0 (70.0, 91.30)	0.732
Lung Function								
FEV1 % predicted (Pre BD) [α]	15	84.96 (15.36)	77.31 (15.35)	**0.025**	37	47.78 (14.35)	56.63 (18.78)	**0.006**
FVC % predicted (Pre BD) [α]	15	98.41 (14.23)	93.48 (17.57)	0.167	37	72.69 (17.55)	76.61 (19.94)	0.197
FEV1/FVC (Pre BD) [α]	15	68.23 (8.91)	67.92 (11.03)	0.893	40	52.88 (12.0)	59.22 (13.08)	**0.002**
FEV1 % predicted (Post BD) [α]	12	93.69 (10.69)	84.06 (16.07)	**0.027**	29	55.44 (13.26)	65.46 (18.43)	**0.004**
FVC % predicted (Post BD) [α]	12	104.65 (15.18)	94.71 (17.47)	**0.023**	29	81.90 (16.62)	84.94 (18.41)	0.259
FEV1/FVC (Post BD) [α]	12	70.36 (7.42)	72.27 (11.36)	0.313	30	53.23 (10.71)	60.58 (12.18)	**0.0007**
Medication Use								
OCS use[¥]	16	9 (56.25%)	10 (62.50%)	1.0	55	26 (47.27%)	20 (36.36%)	**0.031**
OCS dose (mg/day) [β]	7	10 (5, 25), 2.5-25	10 (5, 12.5), 2.5-25	0.159	20	10 (9, 13.75), 2-25	10 (5, 25), 2-75	0.552
ICS dose (BDPmcg/day) [β], range	16	2000 (1440, 3320)	2000 (1600, 2820)	0.703	47	2000 (1600, 2880)	2000 (1600, 3280)	0.172
Long Acting Muscarinic Antagonist [¥]	17	4 (23.53%)	4 (23.53%)	1.0	55	12 (21.82%)	14 (25.45%)	0.500
Leukotriene Modifier [¥]	16	2 (12.50%)	2 (12.50%)	1.0	55	2 (3.64%)	3 (5.45%)	1.0
Theophylline [¥]	17	0	0	1.0	55	3 (5.45%)	3 (5.45%)	1.0
Asthma Questionnaire Scores								
ACQ5 Score [α]	15	3.32 (1.00)	2.33 (1.03)	**0.004**	51	3.42 (1.02)	2.06 (1.30)	**<0.0001**
AQLQ Activity [α]	5	3.38 (1.47)	4.44 (0.93)	0.256	26	3.76 (1.36)	4.62 (1.22)	**0.007**
AQLQ Symptoms [α]	5	2.82 (1.84)	4.82 (0.81)	0.075	26	3.68 (1.41)	4.53 (1.40)	**0.009**
AQLQ Emotions [α]	5	2.64 (1.68)	4.20 (1.21)	0.130	26	3.29 (1.27)	4.28 (1.51)	**0.007**
AQLQ Environment [α]	5	2.70 (1.32)	4.25 (1.50)	0.183	26	3.56 (1.67)	4.02 (1.74)	0.160
AQLQ Mean Score [α]	5	2.97 (1.58)	4.52 (0.91)	0.115	26	3.63 (1.33)	4.46 (1.30)	**0.008**

[β] median (Q1,Q2), Wilcoxon sign rank test; [α] mean (SD), paired t-test; [¥] n(%), McNemar's chi^2 or exact test.

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e-Table 3: Response to Omalizumab Treatment, Based on Post-Bronchodilator FEV1 and Smoking History.

	Post β2 FEV1% <80% Never smoker				**Post β2 FEV1% < 80% Ever smoker**			
	N	Visit1	Visit 2	P value	N	Visit1	Visit 2	P value
Weight, kg; [β]	36	78.0 (68.75, 94.40)	78.25 (67.75, 91.0)	0.994	11	91.30 (78.0, 97.0)	90.0 (78.0, 97.0)	0.582
Lung Function								
FEV1 % predicted (Pre BD) [α]	27	43.77 (12.83)	56.74 (19.31)	**0.001**	6	62.78(13.31)	54.50 (19.99)	0.214
FVC % predicted (Pre BD) [α]	27	68.79 (16.66)	76.29 (21.98)	**0.040**	6	87.91 (15.69)	76.72 (17.60)	0.081
FEV1/FVC (Pre BD) [α]	28	51.45 (12.41)	59.60 (12.78)	**0.002**	7	57.92 (9.91)	56.59 (14.02)	0.609
FEV1 % predicted (Post BD) [α]	21	51.91 (12.59)	66.11 (19.95)	**0.001**	5	68.26 (4.08)	67.92 (9.42)	0.950
FVC % predicted (Post BD) [α]	21	79.14 (17.86)	85.51(20.22)	0.059	5	92.57 (11.15)	87.73 (15.37)	0.403
FEV1/FVC (Post BD) [α]	22	51.91 (10.78)	61.05 (12.66)	**0.001**	5	57.90 (6.79)	60.40 (5.58)	0.306
Medication Use								
OCS use[¥]	36	15 (41.67%)	11 (30.56%)	0.125	11	7 (63.64%)	5 (45.45%)	0.500
OCS dose (mg/day), [β]	11	10 (10, 25), 2-25	12.5 (10, 25), 2-50	0.946	5	10 (10, 12.5), 10-25	25 (10, 25), 10-75	0.160
ICS dose (BDPmcg/day) [β] range	32	2000 (1600, 2760)	2140 (2000, 3240)	0.135	10	2000 (1600, 3600)	2000 (1600, 3600)	0.318
Long Acting Muscarinic Antagonist[¥]	36	8 (22.22%)	8 (22.22%)	1.0	11	2 (18.18%)	3 (27.27%)	1.0
Leukotriene Modifier[¥]	36	1 (2.78%)	1 (2.78%)	1.0	11	1 (9.09%)	2 (18.18%)	1.0
Theophylline[¥]	36	3 (8.33%)	3 (8.33%)	1.0	11	0	0	1.0
Asthma Questionnaire Scores								
ACQ5 Score [α]	32	3.52 (1.01)	1.92 (1.19)	**<0.0001**	11	3.73 (0.62)	2.60 (1.71)	**0.029**
AQLQ Activity [α]	22	3.96 (1.34)	4.69 (1.30)	**0.042**	3	2.18 (0.24)	4.03 (0.37)	**0.032**
AQLQ Symptoms [α]	22	3.93 (1.39)	4.70 (1.37)	**0.035**	3	2.19 (0.38)	3.17 (1.28)	0.311
AQLQ Emotions [α]	22	3.48 (1.27)	4.39 (1.59)	**0.031**	3	2.0 (0.53)	3.27 (0.61)	**0.019**
AQLQ Environment [α]	22	3.77 (1.69)	4.10 (1.84)	0.375	3	1.92 (0.38)	3.17 (0.88)	0.185
AQLQ Mean Score [α]	22	3.85 (1.32)	4.57 (1.34)	**0.041**	3	2.13 (0.11)	3.48 (0.72)	0.067

[β] median (Q1,Q2), Wilcoxon sign rank test; [α] mean (SD), paired t-test; [¥] n(%), McNemar's chi^2 or exact test.

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