Word Count (abstract): 248

Word Count (text): 2627

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

Short Title (50 characters): Omalizumab in Asthma-COPD Overlap

Authors: Steven Maltby PhD[1,2,3], Peter G. Gibson MBBS FRACP FThorSoc[1,2,3,4], Heather Powell MMedSc[2,3,4] and Vanessa M. McDonald PhD, B. Nurs. RN [1,2,3,4]

Affiliations: [1]National Health and Medical Research Council Centre of Excellence in Severe Asthma, [2]Priority Research Centre for Healthy Lungs, the University of Newcastle, [3]Hunter Medical Research Institute, [4]Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, Australia,

***Corresponding Author:** Vanessa M. McDonald, Centre of Excellence in Severe Asthma, Priority Research Centre for Healthy Lungs and Hunter Medical Research Institute, Faculty of Health and Medicine, The University of Newcastle, Level 2 West Wing, Locked Bag 1000, Newcastle, New Lambton, NSW 2305, Australia. Email: vanessa.mcdonald@newcastle.edu.au

Conflict of Interest Statements: SM has been supported by fellowships from the Canadian Institutes of Health Research (CIHR) and The University of Newcastle and is supported by the NHMRC Centre of Excellence in Severe Asthma. PGG holds an NHMRC Practitioner Fellowship, has participated in

educational symposia funded by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Novartis, and has participated in studies funded by GlaxoSmithKline and AstraZeneca. HP has no conflicts to declare. VMM is supported by an NHMRC TRIP fellowship, has participated in educational symposia funded by GlaxoSmithKline, AstraZeneca, Menarini, Boehringer Ingelhiem and Novartis, has participated in studies funded by GlaxoSmithKline and advisory boards for GlaxoSmithKline, Novartis, AstraZeneca and Menarini.

Funding Information: The Australian Xolair Registry was supported by Novartis Pharmaceuticals Australia Pty Ltd, as an Investigator-sponsored study. Preparation of this article was made possible through funding from the National Health and Medical Research Council (NHMRC) Centre of Excellence in Severe Asthma (APP1078579, www.severeasthma.org.au).

Prior Abstract Publication / Presentation: N/A

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.

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.

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.

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).

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.

Acknowledgements

Members of the Australian Xolair registry team are: Peter G Gibson, Helen Reddel, Vanessa M McDonald, Guy Marks, Christine Jenkins, Andrew Gillman, John Upham, Michael Sutherland, Janet Rimmer, Frank Thien, Greg P Katsoulotos, Matthew Cook, Ian Yang, Connie Katelaris, Simon Bowler, David Langton, Paul Robinson, Craig Wright, Veronica Yozghatlian, Scott Burgess, Pathmanathan Sivakumaran, Adam Jaffe, Jeff Bowden, Peter AB Wark, Kwok Y Yan, Vicky Kritikos, Matthew Peters, Mark Hew, Ali Aminazad, Michael Bint, Michael Guo

The Australian Xolair Registry was supported by Novartis Pharmaceuticals Australia Pty Ltd, as an Investigator-sponsored study. Preparation of this article was made possible through funding from the National Health and Medical Research Council (NHMRC) Centre of Excellence in Severe Asthma (APP1078579, www.severeasthma.org.au).

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.

Financial/Non-Financial Disclosures

SM has been supported by fellowships from the Canadian Institutes of Health Research (CIHR) and the University of Newcastle and is supported by the NHMRC Centre of Excellence in Severe Asthma. PGG holds an NHMRC Practitioner Fellowship, has participated in educational symposia funded by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Novartis, and has participated in studies funded by GlaxoSmithKline and AstraZeneca. HP has no conflicts to declare. VMM is supported by an NHMRC TRIP fellowship, has participated in educational symposia funded by GlaxoSmithKline, AstraZeneca, Menarini, Boehringer Ingelhiem and Novartis, has participated in studies funded by GlaxoSmithKline and advisory boards for GlaxoSmithKline, Novartis, AstraZeneca and Menarini.

References

1. Reddel HK, Bateman ED, Becker A, et al. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015; 46(3): 622-639
2. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013; 187(4): 347-365
3. McDonald VM, Higgins I, Gibson PG. Managing older patients with coexistent asthma and chronic obstructive pulmonary disease: diagnostic and therapeutic challenges. *Drugs Aging* 2013; 30(1): 1-17
4. Gibson PG, McDonald VM. Asthma-COPD overlap 2015: now we are six. *Thorax* 2015; 70(7): 683-691
5. Miravitlles M, Soriano JB, Ancochea J, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respir Med* 2013; 107(7): 1053-1060
6. Hardin M, Cho M, McDonald ML, et al. The clinical and genetic features of COPD-asthma overlap syndrome. *Eur Respir J* 2014; 44(2): 341-350
7. Menezes AM, Montes de Oca M, Perez-Padilla R, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. *Chest* 2014; 145(2): 297-304
8. GINA, GOLD. Diagnosis of Diseases of Chronic Airflow Limitation: Asthma COPD and Asthma-COPD Overlap Syndrome (ACOS): GINA / GOLD Report, 2015
9. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016; 47(2): 410-419
10. Grainge CL, Maltby S, Gibson PG, Wark PA, McDonald VM. Targeted therapeutics for severe refractory asthma: monoclonal antibodies. *Expert Rev Clin Pharmacol* 2016; 9(7): 927-941
11. Jamieson DB, Matsui EC, Belli A, et al. Effects of allergic phenotype on respiratory symptoms and exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 188(2): 187-192
12. Neves MC, Neves YC, Mendes CM, et al. Evaluation of atopy in patients with COPD. *J Bras Pneumol* 2013; 39(3): 296-305
13. Renkema TE, Kerstjens HA, Schouten JP, Vonk JM, Koeter GH, Postma DS. The importance of serum IgE for level and longitudinal change in airways hyperresponsiveness in COPD. *Clin Exp Allergy* 1998; 28(10): 1210-1218
14. Travers J, Marsh S, Caldwell B, et al. External validity of randomized controlled trials in COPD. *Respir Med* 2007; 101(6): 1313-1320
15. Travers J, Marsh S, Williams M, et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? *Thorax* 2007; 62(3): 219-223
16. Bardelas J, Figliomeni M, Kianifard F, Meng X. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. *J Asthma* 2012; 49(2): 144-152
17. Chanez P, Contin-Bordes C, Garcia G, et al. Omalizumab-induced decrease of FcxiRI expression in patients with severe allergic asthma. *Respir Med* 2010; 104(11): 1608-1617

18. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001; 108(2): 184-190
19. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011; 154(9): 573-582
20. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011; 364(11): 1005-1015
21. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol* 2013; 131(1): 110-116 e111
22. Holgate ST, Chuchalin AG, Hebert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004; 34(4): 632-638
23. Ohta K, Miyamoto T, Amagasaki T, Yamamoto M, Study G. Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma. *Respirology* 2009; 14(8): 1156-1165
24. Soler M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001; 18(2): 254-261
25. Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004; 59(7): 709-717
26. Massanari M, Holgate ST, Busse WW, Jimenez P, Kianifard F, Zeldin R. Effect of omalizumab on peripheral blood eosinophilia in allergic asthma. *Respir Med* 2010; 104(2): 188-196
27. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; 60(3): 309-316
28. Milgrom H, Fick RB, Jr., Su JQ, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 Study Group. *N Engl J Med* 1999; 341(26): 1966-1973
29. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001; 108(2): E36
30. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol* 2009; 124(6): 1210-1216
31. Gibson PG, Taramarcaz P, McDonald VM. Use of Omalizumab in a Severe Asthma Clinic. *Respirology* 2007; 12 (Suppl. 3): S35–S44
32. Abraham I, Alhossan A, Lee CS, Kutbi H, MacDonald K. "Real-life" effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review. *Allergy* 2015
33. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev* 2014; 1CD003559

34. Djukanovic R, Wilson SJ, Kraft M, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004; 170(6): 583-593
35. Oliver JM, Tarleton CA, Gilmartin L, et al. Reduced FcepsilonRI-mediated release of asthma-promoting cytokines and chemokines from human basophils during omalizumab therapy. *Int Arch Allergy Immunol* 2010; 151(4): 275-284
36. Schroeder JT, Bieneman AP, Chichester KL, et al. Decreases in human dendritic cell-dependent T(H)2-like responses after acute in vivo IgE neutralization. *J Allergy Clin Immunol* 2010; 125(4): 896-901 e896
37. Chan MA, Gigliotti NM, Dotson AL, Rosenwasser LJ. Omalizumab may decrease IgE synthesis by targeting membrane IgE+ human B cells. *Clin Transl Allergy* 2013; 3(1): 29
38. Gibson PG, Reddel H, McDonald VM, et al. Effectiveness and response predictors of omalizumab in a severe allergic asthma population with a high prevalence of comorbidities: the Australian Xolair Registry. *Intern Med J* 2016n/a-n/a
39. Hew M, Gillman A, Sutherland M, et al. Real-life effectiveness of omalizumab in severe allergic asthma above the recommended dosing range criteria. *Clin Exp Allergy* 2016
40. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005; 99(5): 553-558
41. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. *Chest* 1999; 115(5): 1265-1270
42. Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM, British Thoracic Society Difficult Asthma N. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. *Thorax* 2010; 65(9): 787-794
43. Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2007; 119(2): 405-413
44. Yalcin AD, Celik B, Yalcin AN. Omalizumab (anti-IgE) therapy in the asthma-COPD overlap syndrome (ACOS) and its effects on circulating cytokine levels. *Immunopharmacol Immunotoxicol* 2016; 38(3): 253-256
45. Tat TS, Cilli A. Omalizumab treatment in asthma-COPD overlap syndrome. *J Asthma* 20161-3
46. Korn S, Thielen A, Seyfried S, Taube C, Kornmann O, Buhl R. Omalizumab in patients with severe persistent allergic asthma in a real-life setting in Germany. *Respir Med* 2009; 103(11): 1725-1731
47. Brightling CE, Bleecker ER, Panettieri RA, Jr., et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. *Lancet Respir Med* 2014; 2(11): 891-901
48. Celedon JC, Speizer FE, Drazen JM, et al. Bronchodilator responsiveness and serum total IgE levels in families of probands with severe early-onset COPD. *Eur Respir J* 1999; 14(5): 1009-1014

49. de Jong JW, van der Belt-Gritter B, Koeter GH, Postma DS. Peripheral blood lymphocyte cell subsets in subjects with chronic obstructive pulmonary disease: association with smoking, IgE and lung function. *Respir Med* 1997; 91(2): 67-76
50. Jin J, Liu X, Sun Y. The prevalence of increased serum IgE and Aspergillus sensitization in patients with COPD and their association with symptoms and lung function. *Respir Res* 2014; 15130
51. Masuko H, Sakamoto T, Kaneko Y, et al. Lower FEV1 in non-COPD, nonasthmatic subjects: association with smoking, annual decline in FEV1, total IgE levels, and TSLP genotypes. *Int J Chron Obstruct Pulmon Dis* 2011; 6181-189
52. Sherrill DL, Lebowitz MD, Halonen M, Barbee RA, Burrows B. Longitudinal evaluation of the association between pulmonary function and total serum IgE. *Am J Respir Crit Care Med* 1995; 152(1): 98-102

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.

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

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

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

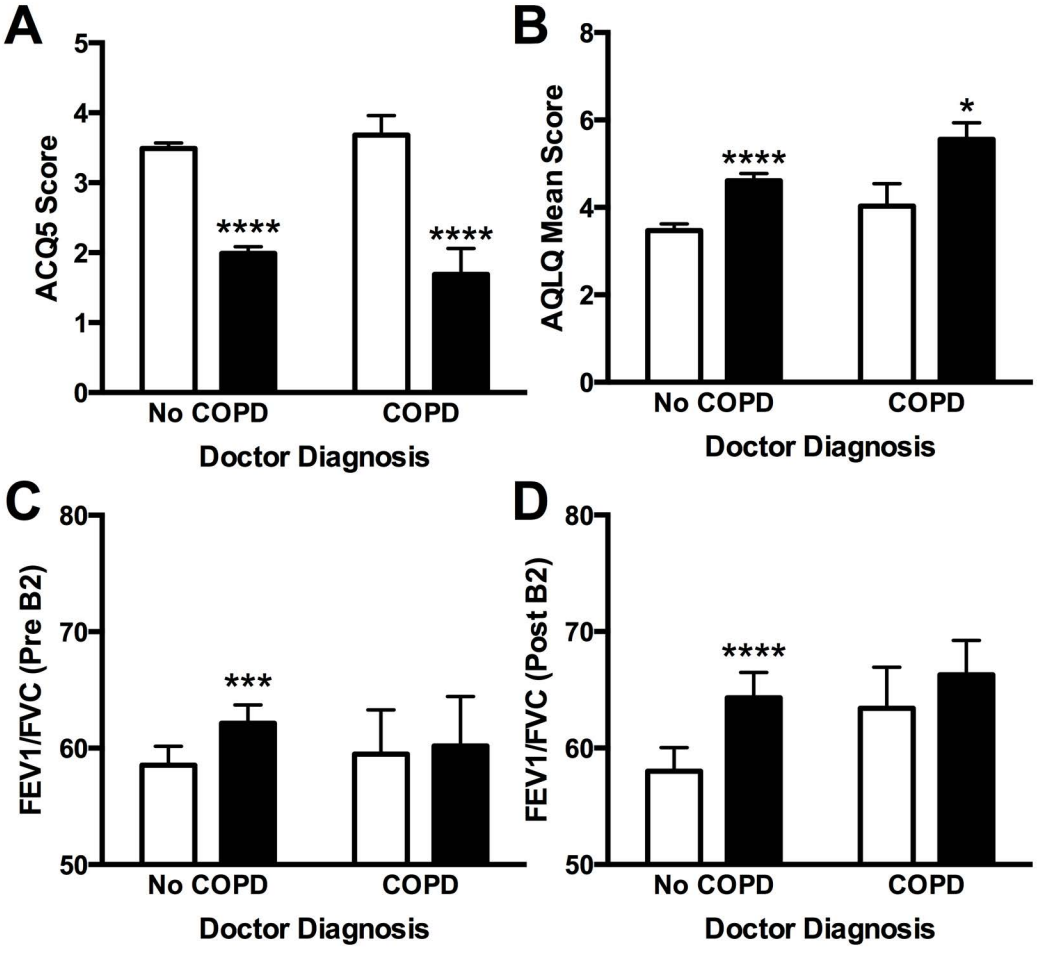
Table 3: Baseline Patient Characteristics, Based on Post-BD FEV_1 and Smoking History.

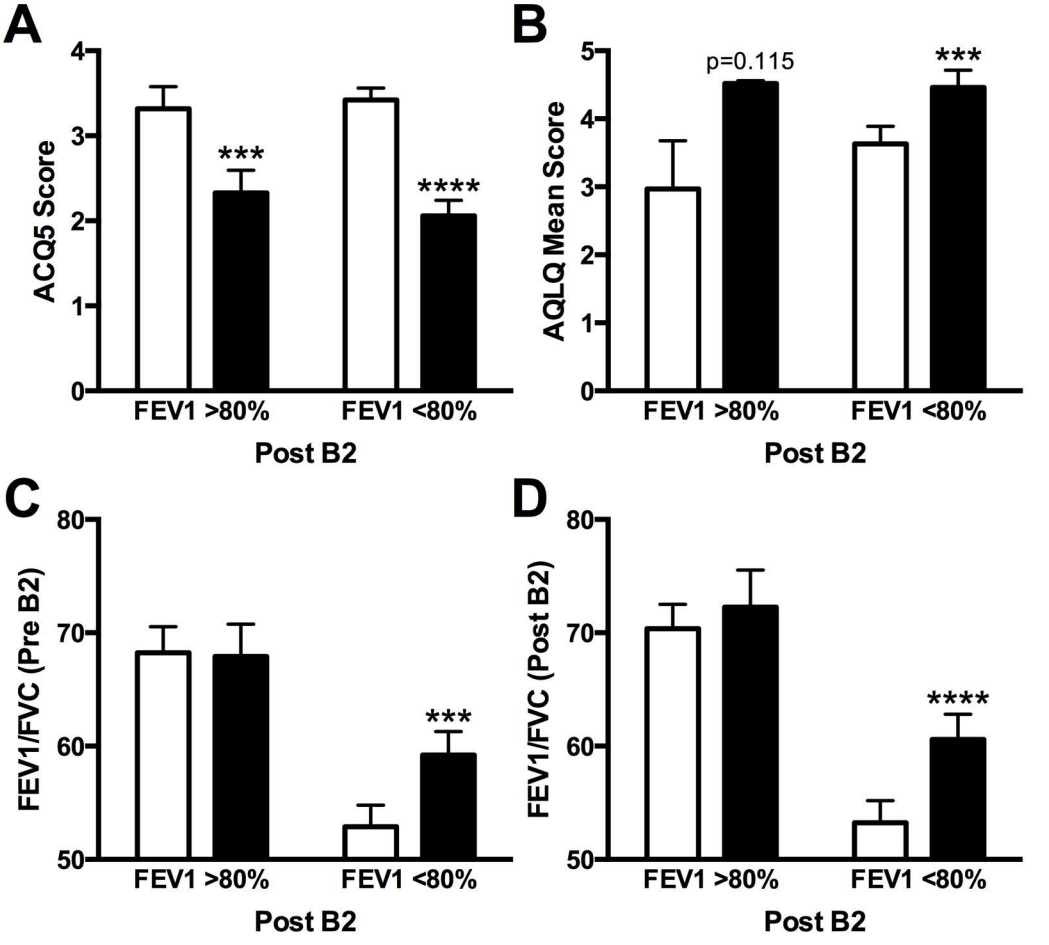
	Post β2 FEV1% ≥ 80% N=17	Post β2 FEV1% < 80%		P value
		Never smoker N=36	Ever smoker N=11	
Age [α]	49.2 (17.9)	49.8 (14.1)	56. 9 (11.4)	0.334
Male[¥]	4 (23.5%)	18 (50.0%)	3 (27.3%)	0.136
Smoking:[¥]				**<0.0001**
Never	14 (82.4%)	36 (100%)	0	
Current	0	0	2 (18.2%)	
Ex	3 (17.7%)	0	9 (81.8%)	
Pack years [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**

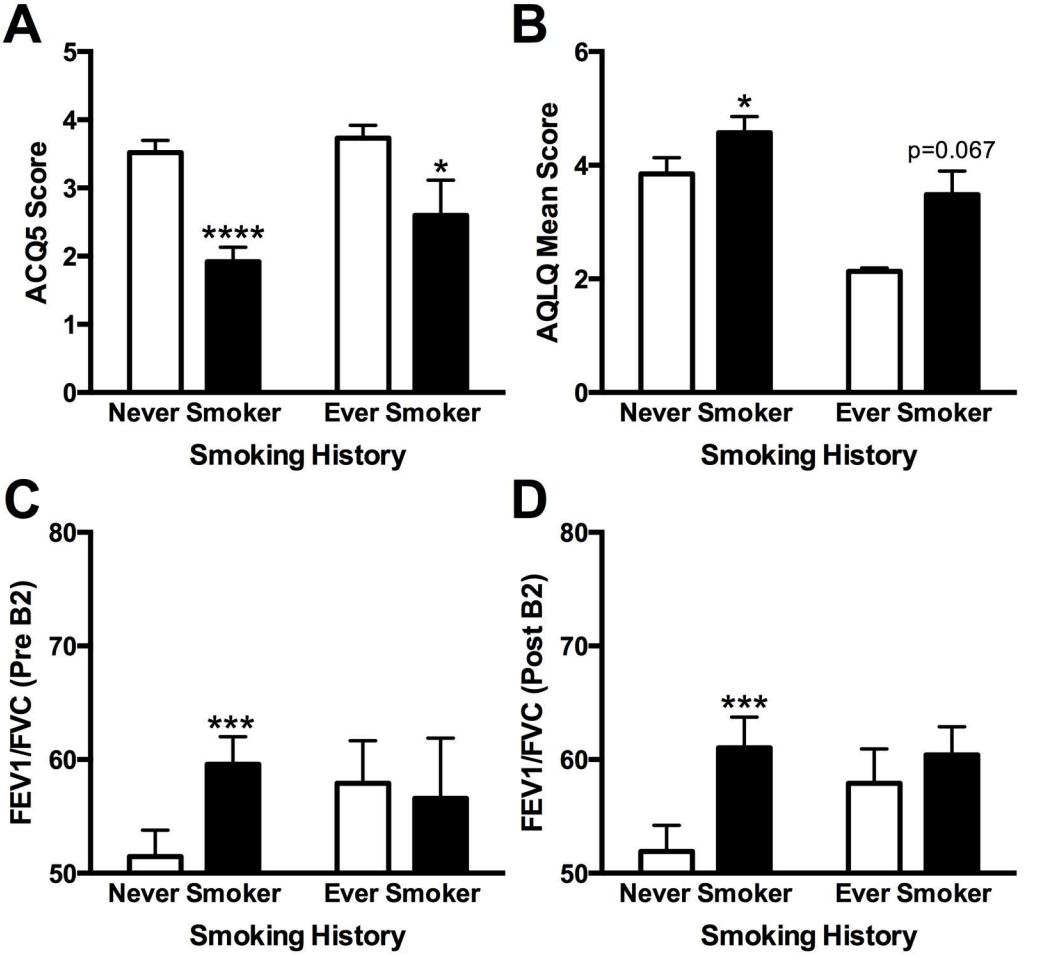
FVC % predicted (Post BD) [α]	105.5 (13.6)	77.5 (17.7) [≠]	84.3 (14.6) [≠]	**<0.0001**
FEV1/FVC (Post BD) [α]	69.1 (7.7)	53.6 (11.7) [≠]	55.7 (8.6) [≠]	**<0.0001**
Medication Use				
OCS use[¥]	9 (56.3%)	16 (44.4%)	7 (63.6%)	0.510
OCS dose (mg/day) [β], range	10 (7.50, 18.75),2.5-25	11.3 (10, 25), 2-50	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

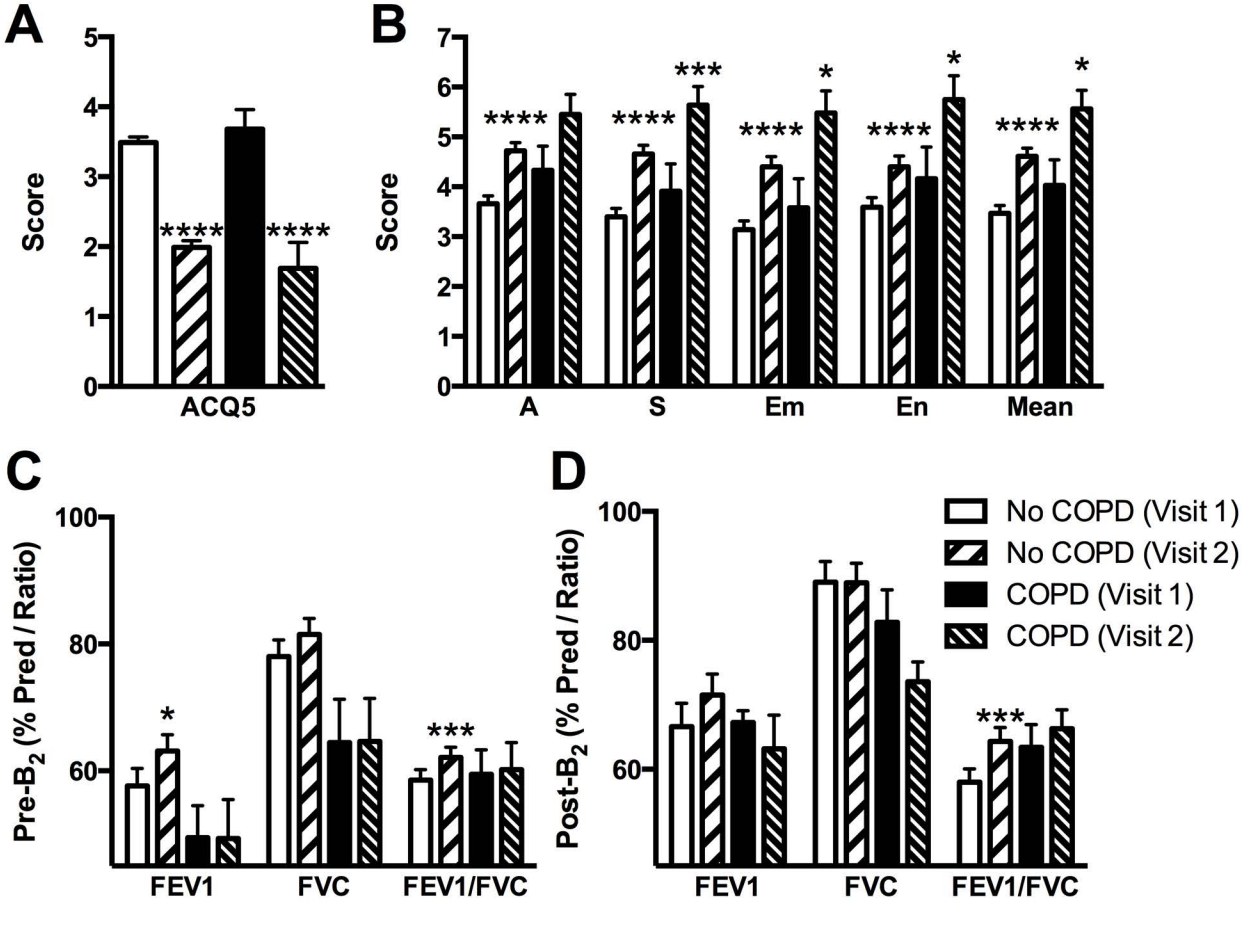
[α] mean (SD), one-way ANOVA; [β] median (Q1,Q2), Kruskall Wallis test; [¥] n(%),chi2 or Fisher's exact test.

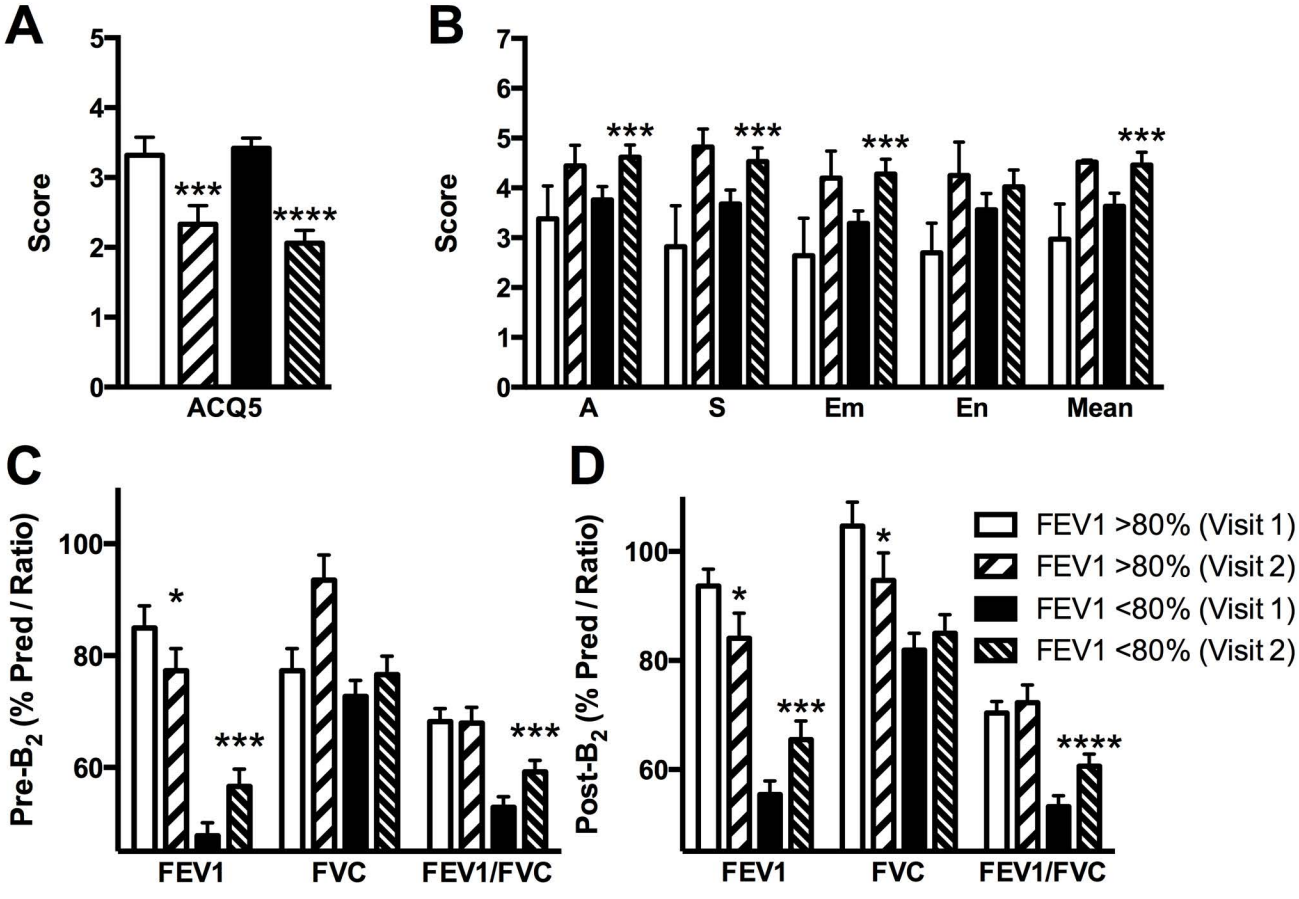
[≠]post hoc sig vs Post β2 FEV1% ≥ 80%; [μ] post hoc sig vs Post β2 FEV1% < 80% & never smoker

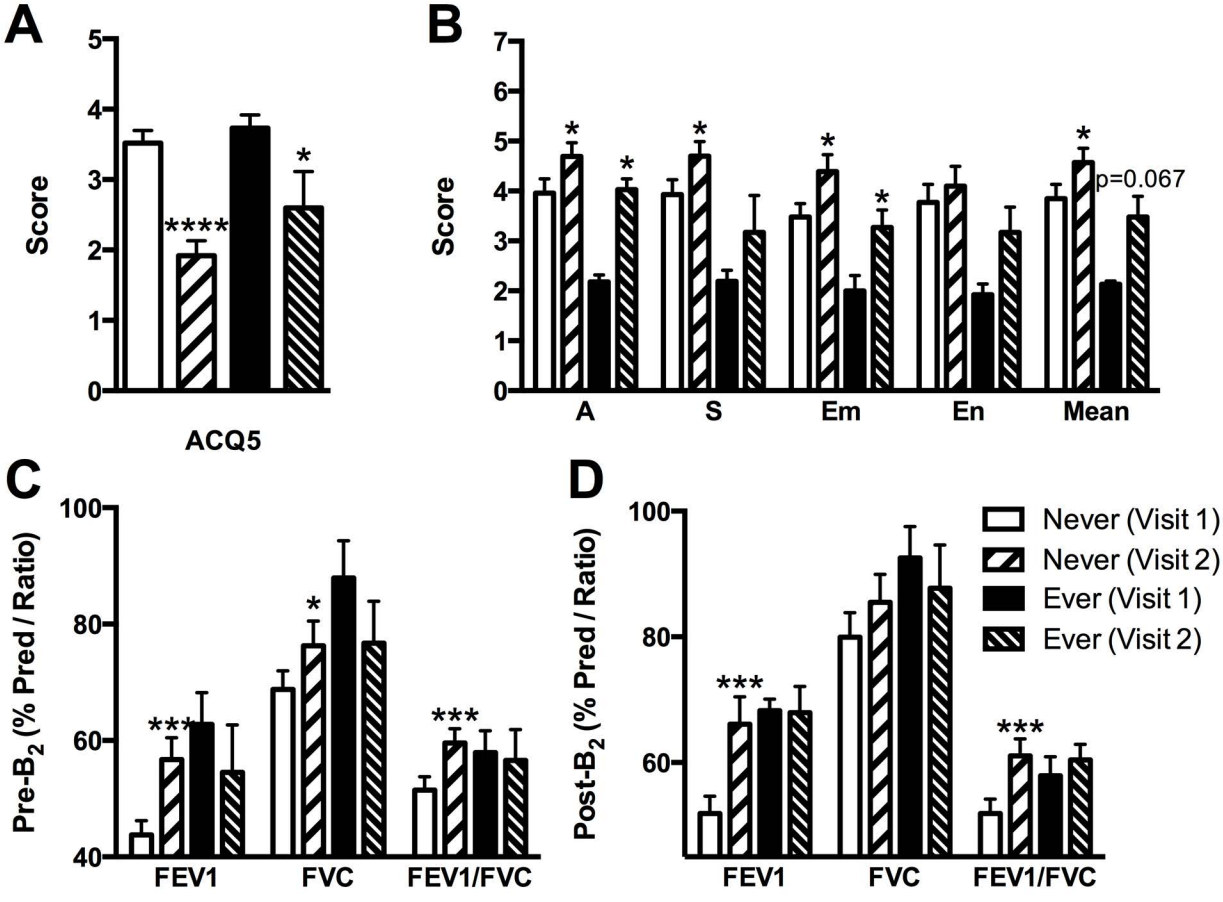

A
ACQ5 Score
5
4
3
2
1
0
****
****
No COPD
COPD
Doctor Diagnosis
B
AQLQ Mean Score
8
6
4
2
0
****
*
No COPD
COPD
Doctor Diagnosis
C
FEV1/FVC (Pre B2)
80
70
60
50
***
No COPD
COPD
Doctor Diagnosis
D
FEV1/FVC (Post B2)
80
70
60
50
****
No COPD
COPD
Doctor Diagnosis


A
ACQ5 Score
4
3
2
1
0
***
****
FEV1 >80%
FEV1 <80%
Post B2
B
AQLQ Mean Score
5
4
3
2
1
0
p=0.115
***
FEV1 >80%
FEV1 <80%
Post B2
C
FEV1/FVC (Pre B2)
80
70
60
50
***
FEV1 >80%
FEV1 <80%
Post B2
D
FEV1/FVC (Post B2)
80
70
60
50
****
FEV1 >80%
FEV1 <80%
Post B2


A
ACQ5 Score
5
4
3
2
1
0
****
*
Never Smoker
Ever Smoker
Smoking History
B
AQLQ Mean Score
6
4
2
0
*
p=0.067
Never Smoker
Ever Smoker
Smoking History
C
FEV1/FVC (Pre B2)
80
70
60
50
***
Never Smoker
Ever Smoker
Smoking History
D
FEV1/FVC (Post B2)
80
70
60
50
***
Never Smoker
Ever Smoker
Smoking History


A
Score
5
4
3
2
1
0
****
****
ACQ5
B
Score
7
6
5
4
3
2
1
0
****
****
****
****
****
***
*
*
*
A
S
Em
En
Mean
C
Pre-B2 (% Pred / Ratio)
100
80
60
*
***
FEV1
FVC
FEV1/FVC
D
Post-B2 (% Pred / Ratio)
100
80
60
***
FEV1
FVC
FEV1/FVC
No COPD (Visit 1)
No COPD (Visit 2)
COPD (Visit 1)
COPD (Visit 2)


A
Score
5
4
3
2
1
0
***
****
ACQ5
B
Score
7
6
5
4
3
2
1
0
***
***
***
***
A
S
Em
En
Mean
C
Pre-B2 (% Pred / Ratio)
100
80
60
*
***
***
FEV1
FVC
FEV1/FVC
D
Post-B2 (% Pred / Ratio)
100
80
60
*
***
*
****
FEV1
FVC
FEV1/FVC
FEV1 >80% (Visit 1)
FEV1 >80% (Visit 2)
FEV1 <80% (Visit 1)
FEV1 <80% (Visit 2)


A
Score
ACQ5
****
*
B
Score
A
S
Em
En
Mean
p=0.067
C
Pre-B2 (% Pred / Ratio)
FEV1
FVC
FEV1/FVC
***
*
D
Post-B2 (% Pred / Ratio)
Never (Visit 1)
Never (Visit 2)
Ever (Visit 1)
Ever (Visit 2)