

Early View

Research letter

Impact of prior smoking exposure and COPD comorbidity on treatment response to monoclonal antibodies in patients with severe asthma

Heba Morobeid, Carmen Pizarro, Leonie Biener, Gudrun Ulrich-Merzenich, Daniel Kütting, Georg Nickenig, Dirk Skowasch

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Impact of prior smoking exposure and COPD comorbidity on treatment response to monoclonal antibodies in patients with severe asthma

To the Editor:

Despite the prognostic role of smoking in asthma (1), clinical studies of asthma usually exclude current smokers or ex-smokers with a smoking history of >10 pack-years (2-5). Specifically, the role of humanised monoclonal antibody therapy in patients with severe asthma and prior smoking exposure has not been studied, however, these drugs are used in patients with severe asthma and a history of smoking (6-9). The aim of the present study was to evaluate in a real-world setting how a history of smoking and comorbid chronic obstructive pulmonary disease (COPD) affect the clinical outcome of patients suffering from severe asthma that are treated with monoclonal antibodies.

This is a single centre, prospective and observational cohort study conducted at the Department of Pneumology of the University Hospital Bonn (Bonn, Germany). Patients (n=158) with severe asthma, based on GINA recommendations (10) that now require antibody treatment, were included from November 2017 to April 2020. As suggested by the GINA recommendations, treatment was optimized to include smoking cessation three months before evaluation of the antibody treatment. Active smokers were excluded from the study. The study had the approval of the local ethics committee. We divided patients into two groups according to their history of smoking: >10 pack-years (ex-smokers) or less (non-smokers). We evaluated the clinical response of patients to the newly-initiated antibody therapies from baseline to follow-up after 6±3 months on the therapy. We considered it to be a clinical improvement if the patient had an increase in the Asthma Control Test (ACT) score ≥ 4 points (11), a decrease in the acute exacerbation rate of 50% (12) or improvement of lung function indicated by an increase of FEV1 $\geq 12\%$ or ≥ 200 ml (12). In addition, non-contrast chest CT scans were obtained with multidetector CT scanners (≥ 128 rows) in 47 patients. Automated emphysema analysis was performed using commercially available software (IntelliSpace Portal, Philips Healthcare, Best, The Netherlands) in order to calculate the emphysema ratios. Lung parenchyma was considered emphysematous when it showed attenuation values of less than -950 Hounsfield units at inspiration (13,14). An emphysema ratio was calculated for each LDCT dataset and was defined as the percentage of lung volume with emphysema divided by the total lung volume. Continuous variables were evaluated by using a paired t-test, categorical parameters by using Pearson's Chi-squared test and non-parametric values by using a Mann-Whitney U test. A value of $p < 0.05$ was considered to be statistically significant.

Baseline clinical data for the patients (n=158) are summarized in Table 1. All patients were on high-dose inhaled corticosteroids (1918 ± 163 vs. 1890 ± 176 μ g beclomethasone dipropionate, deemed equivalent in the non-smoking compared to the ex-smoking groups) and long-acting beta-2 agonists;

95% were on long-acting muscarinic antagonists, while 65% of patients required oral corticosteroid (OCS) therapy. At baseline, clinical and laboratory parameters such as fractional exhaled nitric oxide (45.31 ± 48.42 ppb), blood eosinophils (492.16 ± 382.86 per μl) and immunoglobulin E (557.26 ± 828.20 IU/ml) were similar between the two groups. The groups differed significantly in sex (74% vs. 44% female in the non-smoking compared to the ex-smoking group, $p < 0.001$), age (51 ± 15 years vs. 59 ± 11 years, $p = 0.002$) and pack-years (5 ± 2 vs. 28 ± 17 , $p < 0.001$). All patients received antibody therapies upon inclusion in the study, which did not differ between the two patient groups (29% omalizumab, 32% benralizumab, 25% dupilumab, 14% mepolizumab, 1% reslizumab). 18 patients were excluded from the analysis because they dropped out before reaching 4 months of treatment (12 in the non-smoking and 6 in the ex-smoking group); Of these, 12 discontinued treatment owing to a lack of clinical improvement (9 vs. 3), 4 owing to a lack of tolerability (2 from each group) and 2 patients were lost to clinical follow-up (1 from each group). Following the initiation of antibody treatment, overall asthma control improved significantly, with an increase of the ACT score ≥ 4 points in 71% of the patients. Furthermore, an 89% reduction in the annualized exacerbation rate was achieved and a relevant improvement of lung function was seen in 38% of cases; OCS consumption decreased by 67%, and 68% of patients no longer required OCS. Again, these parameters were similar between the two groups (Table 1). Single response criteria were fulfilled in all 158 cases (100%), and all criteria were fulfilled in 42 cases (27%). The quantification of emphysema by CT showed that ex-smoking patients had a significantly higher emphysema ratio, corresponding clinically to a rate of 50% COPD comorbidity in the ex-smoking group. Again, there was no difference in the treatment responses in patients with emphysema and/or COPD. In addition, there was no correlation between the emphysema score and changes in ACT ($r = 0.070$; $p = 0.640$), exacerbation rate ($r = -0.041$; $p = 0.782$), OCS use ($r = 0.075$; $p = 0.615$) or FEV1 increase ($r = -0.212$; $p = 0.153$).

This is, to our knowledge, the first clinical observational study about the association between smoking history and the responsiveness of patients with severe asthma to GINA treatment step 5 add-on antibody therapy. It is well known that cigarette smoking is common in adults with asthma and is associated with increased morbidity and mortality (1). The recent SHARP study on patients with severe asthma documents a smoking history in Europe between 10.8% and 41.3%. In Germany, 2.4% of such patients are current smokers and 37.8 % are ex-smokers, with an average of 12.5 pack-years overall. However, the effects of treatment were not analysed in the SHARP study (9). The treatment response found in our study is comparable to real-world data (6-8), which already showed patient responses in the real-world are similar to those in randomized controlled trials (although our study had a more stringent patient selection) (6-8). In our study, ex-smokers with severe asthma benefited similarly compared to non-smokers with severe asthma, in all of the selected endpoints. The proportion of men in the ex-smoker group was higher despite the higher proportion of women

seen across clinical trials and registries of patients with asthma, which demonstrates that smoking is still more common in males. The ex-smoker patient group was also significantly older compared to the non-smoker group. Smoking is the major factor in the development of COPD and differentiating between patients with asthma and COPD can be difficult; we used the new GINA/GOLD recommendations from 2020 for the diagnosis of asthma–COPD overlap (ACO) (10). Accordingly, 50% of ex-smokers suffering from severe asthma fulfilled the clinical criteria for the diagnosis of ACO. Of interest, this subgroup of patients with COPD comorbidity, in addition to the patients with emphysema, also showed a similar response to the antibody treatments.

Our study had both strengths and limitations. The strengths included a clinically detailed characterization of prospectively enrolled patients with severe asthma, a detailed documentation of the response to newly prescribed antibody treatments, the low number of patients who were lost to follow-up and the “real-world” setting of the study; limitations included the small sample size, the short follow-up interval and the registry nature of the data source, which obviously does not reach the same quality of a randomized clinical trial.

In conclusion, this real-world study extends previously published reports on the response of patients with severe asthma to antibody treatments, particularly by including patients with a history of smoking. We found that antibody treatments, when added to standard asthma therapies, are as efficacious in ex-smokers suffering from severe asthma as they are in non-smokers, by improving the asthma control, exacerbation rate and lung function of these patients. In conclusion, our data suggest that patients suffering from severe asthma should benefit from antibody treatment, irrespective of their history of smoking. However, further placebo-controlled studies in this patient collective are warranted.

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Heba Morobeid¹, Carmen Pizarro¹, Leonie Biener¹, Gudrun Ulrich-Merzenich², Daniel Kütting³, Georg Nickenig¹, Dirk Skowasch¹

The first two authors contributed equally to this work.

¹Dept. of Internal Medicine II - Pneumology/Cardiology, University Hospital Bonn, Bonn, Germany,

²Dept. of Internal Medicine III – Oncology, University Hospital Bonn, Bonn, Germany, ³Dept. of Radiology, University Hospital Bonn, Bonn, Germany

Correspondence: Dirk Skowasch, Dept. of Internal Medicine II - Pneumology/Cardiology, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany

References:

1. Thomson NC. Asthma and smoking-induced airway disease without spirometric COPD. *Eur Resp J* 2017; 49: 1602061.
2. Hanania NA, Wenzel S, Rosén K, *et al.* Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Crit Care Med* 2013; 15: 804-811.
3. Bleecker ER, FitzGerald JM, Chanez P, *et al.* Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; 29: 2115-2127.
4. Ortega HG, Liu MC, Pavord ID, *et al.* Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371: 1198-1207.
5. Castro M, Corren J, Pavord ID, *et al.* Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018; 378: 2486-2496.
6. Harrison T, Canonica GW, Chupp G, *et al.* Real-world mepolizumab in the prospective severe asthma REALTI-A study: initial analysis. *Eur Resp J* 2020; 56: 2000151.
7. Kavanagh JE, Hearn AP, Dhariwal J, *et al.* Real-world effectiveness of benralizumab in severe eosinophilic asthma. *Chest* 2021; 159: 496-506.
8. Bousquet J, Humbert M, Gibson PG, *et al.* Real-world effectiveness of omalizumab in severe allergic asthma: a meta-analysis of observational studies. *J Allergy Clin Immunol Pract* 2021; 21: S2213.
9. Van Bragt JJMH, Adcock IM, Bel EHD, *et al.* Characteristics and treatment regimens across ERS SHARP severe asthma registries. *Eur Resp J* 2020; 55: 1901163.
10. Schatz M, Kosinski M, Yaras AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol* 2009; 124: 719-723.
11. Drick N, Seeliger B, Welte T, Fuge J, Suhling H. Anti-IL-5 therapy in patients with severe eosinophilic asthma - clinical efficacy and possible criteria for treatment response. *BMC pulmonary medicine* 2018; 18: 119.
12. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020. Available from: www.ginaasthma.org
13. Fischer AM, Varga-Szemes A, van Assen M *et al.* Comparison of artificial intelligence-based fully automatic chest CT emphysema quantification to pulmonary function testing. *AJR* 2020; 214: 1065-1071.
14. Herth FJF, Slebos DJ, Shah PL, *et al.* Protocol of a Randomized Controlled Study of the PneumRx Endobronchial Coil System versus Standard-of-Care Medical Management in the Treatment of Subjects with Severe Emphysema (ELEVATE). *Respiration* 2019; 98: 512-520.

Legend

	All (n=158)	Ex-smokers (n=48) (30%)	Non-smokers (n=110) (70%)	p-value
Sex, n (%)				
Females	102 (65%)	21 (44%)	81 (74%)	0.010*
Age (y)	53.4 ± 14.67	58.88 ± 11.40	51.07 ± 15.33	0.002*
BMI (kg/m²)	28.56 ± 6.41	28.90 ± 4.89	28.41 ± 6.99	0.060
Duration of the disease (y)	26.47 ± 16.33	24.42 ± 18.65	26.94 ± 15.30	0.045
Pack-years (y)	21.70 ± 18.07	27.98 ± 17.4	4.94 ± 1.83	<0.001*
Comorbidities, n (%)				
COPD	36 (33%)	24 (50%)	12 (11%)	<0.001*
Emphysema	19 (12%)	10 (21%)	9 (8%)	0.017*
Allergy	92 (84%)	27 (56%)	66 (60%)	0.331
Atopic dermatitis	18(16%)	3 (6%)	15 (14%)	0.095
Chronic sinusitis/nasal polyps	70 (64%)	17 (35%)	53 (48%)	0.078
Obstructive sleep apnoea	16 (15%)	8 (17%)	8 (7%)	0.287
Gastro-oesophageal reflux	11 (10%)	3 (6%)	8 (7%)	0.891
Obesity (BMI >30)	17 (15%)	3 (6%)	14 (13%)	0.107
ACT score				
at baseline	12.87 ± 5.45	10.78 ± 4.02	12.11 ± 4.76	0.353
at follow-up	16.50 ± 5.88	16.13 ± 6.03	16.66 ± 5.83	0.568
Δ pre- to post-treatment	4.07 ± 5.71	4.60 ± 6.08	3.83 ± 5.55	0.423
FEV1 (ml)				
at baseline	1.97 ± 0.80	1.66 ± 0.60	2.10 ± 0.84	0.007*
at follow-up	2.11 ± 0.77	1.86 ± 0.68	2.21 ± 0.80	0.263
Δ pre- to post-treatment	0.14 ± 0.42	0.21 ± 0.36	0.12 ± 0.46	0.538
Exacerbation rate				
at baseline	4.08 ± 4.16	4.90 ± 4.05	3.73 ± 4.17	0.598
at follow-up	0.22 ± 0.63	0.25 ± 0.94	0.21 ± 0.43	0.240
Δ pre- to post-treatment	-3.89 ± 4.12	-4.79 ± 4.14	-3.49 ± 4.06	0.518
Regular oral corticosteroid dose (mg/day)				
at baseline	7.15± 8.32	8.33 ± 7.45	6.62 ± 8.67	0.700
at follow-up	2.35 ± 4.76	3.50± 5.48	1.84 ± 4.33	0.170
Δ pre- to post-treatment	-3.91 ± 8.74	-3.79 ± 10.35	-3.97 ± 7.97	0.200

Table 1: Patient characteristics and response to antibody therapy

Data are presented as n, n (%) or mean ± SD. ACT: Asthma control test, BMI: body mass index, COPD: chronic obstructive pulmonary disease, FEV1: forced expiratory volume in 1 second. * significant p-value (<0.05).