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Original research article

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The impact of anti-eosinophilic therapy on exercise capacity and inspiratory muscle strength in patients with severe asthma

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Short title: Anti IL5 antibody therapy and exercise testing

Keywords: severe asthma; mepolizumab; benralizumab; exercise testing; inspiratory pressure.

Introduction

Asthma is a chronic respiratory disease characterized by reversible airflow limitation and heterogeneous symptoms, as wheezing, cough and dyspnea [1]. Some patients can experience exercise limitation due to exertional dyspnea and fatigue, and this is usually associated with worse quality of life (QoL) [2,3]. Exercise limitations can be caused by different underlying mechanisms of the pulmonary, cardiovascular and muscular systems. The pathophysiological mechanisms of exertional dyspnea have been described in detail in chronic obstructive pulmonary disease (COPD) and interstitial lung diseases (ILDs), but limited data are available about exercise limitation in asthma [4,5]. New antibody drugs against interleukin 5 (Il-5) and its receptor (IL5-R) approved in severe asthma demonstrated reduction of exacerbation, corticosteroid sparing and improvement of FEV1 and quality of life [6,7].

A review conducted by Vermeulen et al. identified different factors related to activity limitation in asthmatic patients, as respiratory muscle weakness, deconditioning, ventilator impairment and dynamic hyperinflation [8]. Furthermore, they reported that the administration of bronchodilation therapy prior to exercise testing (CPET) did not improve the exercise capacity. A randomized control trial was conducted by Van der Meer and colleagues to investigate the effect of corticosteroid therapy on dynamic hyperinflation in patients with moderate to severe asthma [9]. The authors found that after two weeks of triamcinolone therapy the degree of dynamic hyperinflation was reduced by 23.2%.

P0.1 is the pressure generated during the first 0.1 second of normal inspiratory effort against occluded airways and it reflects the central ventilatory drive, since the occlusion time is too short to be influenced by muscle weakness or by conscience [10]. The maximal inspiratory pressure (MIP) generated during a maximal inspiration effort against closed airways, is an indicator of respiratory muscles strength and ventilator pump efficiency. Low MIP may be due to submaximal effort, muscular weakness, elevated functional residual capacity (FRC) with hyperinflation and/or neuromuscular diseases [10]. P0.1/MIP ratio was largely studied

as prognostic factor for mechanical ventilation weaning and extubation success. This ratio denotes the balance between the ventilatory drive (respiratory demand) and the muscular strength (the ability of the respiratory system to respond) [11,12].

Yet no data is available about the role of CPET and inspiratory pressure measurement as indicators of clinical improvement or prognostic tools in severe asthmatic patients treated with anti-eosinophil therapy. We combined the exercise test parameters, plethysmography and P0.1 and MIP measurement to assess the impact of anti-IL5 therapy on exercise capacity and respiratory muscle strength in patients affected by severe eosinophilic asthma.

Methods:

Study population and treatment

This prospective observational, monocentric, study was conducted in the Severe Asthma outpatient Clinic of Hanover Medical School (Germany), from April 2018 to June 2019. Patients affected by severe asthma, as defined by ATS/ERS guidelines 2018 [13], treated with either anti-IL5 (mepolizumab) or anti-IL5 receptor (benralizumab) antibodies were included. All patients provided written informed consent to use their medical records with approval of the local institutional review board (9171_BO_K_2020).

Patients underwent CPET before introduction of antibody therapy and after 3 months. Clinical records were screened and all the following parameters available at baseline and at follow up visits at 3 months, 6 months and 12 months were collected: 1) clinical history, socio-demographic data; 2) functional tests such as body plethysmography with P0.1 and MIP measurement and blood gas analysis; 3) blood eosinophil count; 4) Quality of life assessment, performed with Asthma Control Test (ACT) questionnaire, *fig. 1*. All the pulmonary function tests and CPET parameters available were compared across the follow up time.

All patients were treated according to the current guidelines for severe asthma [1,13,14].

All patients included in the study were older than 18 years and naïve from any monoclonal drug for severe asthma for at least 6 months. All patients signed an informed written consent. All patients were able to perform CPET and had no history of heart failure or neuromuscular disorders.

Exercise testing and inspiratory work

Exercise testing was performed using bicycle ergometer by MGC Diagnostics™ with GE eBike. According to patients' fitness status, an optimized ramp was used and equally maintained for the baseline and follow up test. All patients were encouraged to reach maximal exhaustion until symptom-limitation (eg. dyspnea or fatigue) if no other termination criterion was reached before, and we used the BORG dyspnea questionnaire immediately after test-ending. All tests were performed according to current guidelines for CPET [15] with continuous monitoring of 12-lead electrocardiogram, blood pressure and oxygen saturation.

Blood gas analysis was performed through earlobe sting and collection of capillary blood [16].

Plethysmography was performed following the current German recommendations [17] and ERS guidelines [18]. All parameters were recorded, in particular P0.1, which represents the negative airway pressure generated during the first 100 ms of an occluded normal inspiration, and MIP, the maximal inspiratory pressure generated during maximal breathing effort. These values and their index are markers of respiratory muscle strength.

Definitions

Definitions and reference values are settled according to ATS statement 2003 and ERS statement 2019 and reported as percentage of the predicted value (%) [19,20]. The acronyms used replicated the ERS and ATS/ACCS statement glossaries: oxygen uptake at peak exercise (V´O2 peak), carbon dioxide output at peak exercise (V´CO2 peak), anaerobic threshold (AT), ventilation (VE), maximum voluntary ventilation (MVV), inspiratory capacity (IC), ventilatory equivalent for carbon dioxide (VE/V´CO2), respiratory rate (RR), tidal volume

(VT), end-expiratory lung volume (EELV), arterial oxygen saturation as indicated by pulse oximetry (SpO2), partial pressure of oxygen (pO2) and partial pressure of carbon dioxide (pCO2). The consumption of oxygen (V´O2) was always considered corrected for body weight (ml/kg/min).

Normal values were settled as V´O2 peak (ml/kg/min) ≥ 85%, O2 pulse (ml/bpm) ≥ 80%, breathing reserve (BR, VE peak/MVV) < 85%, VE/V´CO2 slope < 35, VT/IC > 0.75. MVV was extrapolated from the FEV1 (35xFEV1). Desaturation was defined as either a reduction of at least 5% of SpO2 during exercise or capillary pO2 < 60 mmHg at blood gas analysis.

Deconditioning was defined as low V´O2 peak with normal or low O2 pulse, no desaturation, and normal breathing reserve. Cardiovascular limitation was distinct by low V´O2 peak and low O2-pulse, normal breathing reserve and no sign of desaturation. Respiratory limitation was characterized by low V´O2 peak, desaturation and/or breathing reserve depletion [21,22].

Dynamic hyperinflation (DH) was defined as elevation of EELV ≥ 0.250 L during exercise and decrease of IC > 0.2 L [10,21]. DH was also ruled out observing the flow-volume loops during the exercise [10,21,23].

Outcomes

At baseline and at every follow up visit, lung function test, ACT questionnaire and clinical assessment were recorded. At least two of the following criteria defined a positive response to monoclonal therapy as defined by Drick et al., 2018 [24]: 1) self-reported clinical improvement in terms of quality of life, physical performance and symptoms control; 2) rise of the predicted value of the Forced Expiratory Volume in the first second (FEV1%) of at least 12% or 200 ml; 3) eosinophil count reduction to < 150 /µL or to < 20% of the baseline value. At 12 months, 2 groups of patients were identified, those who achieved 2 or more goals (*responders*) and those who did not (*non-responders*).

Finally, P0.1 value was compared across two groups: patients who at baseline were under chronic oral corticosteroid therapy (chronic OCS), versus patients who were not (OCS-free).

Statistical analysis

The software IBM SPSS Statistics 27.0 (IBM Corp, Armonk, NY, USA) was used to analyze the data. Non-parametric continuous variables were presented as median (interquartile range, IQR), normal continuous variable as mean (standard deviation, sd) and categorical variables as number and percentage (n, %).

For comparisons of time points, paired T or Wilcoxon test, linear model for repeated measures and Student´s T or Mann-Whitney tests were used as appropriate. All reported p-values are two sided. P-values below 0.05 were considered statistically significant.

Results

A total of 14 patients were enrolled, baseline characteristics were shown in table 1.

Results from CPET showed no significant changes over 3 months in maximum load, V'O2 peak, ventilatory efficiency, respiratory rate, tidal volume or arterial blood pressure. Dynamic hyperinflation could not be found in patients neither before nor after antibody treatment.

Although the mean capillary pO2 value did not differ between the two timepoints, desaturation during exercise was observed in two patients at baseline. After 3 months of therapy, both these subjects experienced a marked improvement in lung function and gas exchanges (respectively, FEV1 raised by 33% and 38% and capillary pO2 at rest raised by 9 mmHg and 6 mmHg) and desaturation was no more detected.

The mean value of the breathing reserve exhaustion reduced significantly from 78% to 60% (p=0.004). Precisely, at baseline 7 (50%) patients showed depleted BR and after 3 months all of them improved.

Furthermore, the mean value of the ventilation per minute at rest reduced significantly from 17 (sd 3) L/min at baseline to 15 (sd 3) L/min after 3 months, p=0.035.

All the detail are shown in *supplementary material*.

The lung function tests improved after the initiation of antibody therapy, data across the 12 months of follow up are presented in *Table 2*.

The inspiratory work and the ventilatory drive (P0.1, MIP and P0.1/MIP ratio) remained unchanged before and after antibody therapy. As response to anti-eosinophilic therapy, the mean number of circulating eosinophils dropped significantly from 905/µL to 35/µL (p=0.001).

Outcome

After 6 months non-response to antibody therapy was diagnosed in one patient, after 12 months non-response was found in 2 (14.3%) patients. The first patient showed significant decrease of circulating eosinophil granulocytes but still suffered from exacerbations, FEV1 remained unchanged and OCS were still needed. The other patient maintained clinical stability until 6 months, then he experienced several exacerbations and FEV1 dropped. After 12 months, both patients were switched to Dupilumab therapy.

Among the overall population, at baseline 10 (71.4%) patients reported at least 2 exacerbations per year, while at 12 months only 4 (28.6%) patients experienced 2 or more exacerbations. One patient withdrew OCS therapy.

Inspiratory pressure and corticosteroid therapy.

P0.1 value was compared between patients with chronic oral corticosteroid therapy (chronic OCS) at baseline and patients without OCS treatment (OCS-free). Both groups were composed of 7 subjects. P0.1 value was higher in the chronic OCS group, although this difference was not significant (p=0.106). MIP value was similar between the two groups (see *Table 3* and *Figure 2*).

Discussion

This is the first study evaluating anti IL5/-R antibodies using CPET and respiratory work tests. Our results demonstrate the subjective improvement along with gain in lung function and gas exchanges after the initiation of anti-eosinophilic therapy, in line with previous studies on mepolizumab and benralizumab [6,7]. In addition, despite the small number of participants, we found hints that OCS does influence the inspiratory muscle strength.

The treatment with anti-eosinophilic antibodies did not improve the exercise performance in terms of V´O2 peak or work load. This finding is in contrast with the manuscript by Schäper and colleagues, who studied a cohort of severe asthmatic patients that underwent Omalizumab therapy compared to severe asthma patients not treated with antibodies [25]. This difference could depend on the deconditioned performance status of the antibody treatment group, which showed a baseline V'O2 peak of 13.8 that increased to 16.8 ml/kg/min ($p<0.05$). The control group had a median V´O2 peak of 19.4 and 18.8 ml/kg/min in follow up. That values were comparable to our patients before antibody initiation. The relatively high oxygen uptake of the control group or our patients left no room for further improvement. In our cohort, the mean V´O2 peak value was 19 (sd 4.7) ml/kg/min, indicative of quite fit patients. In line with Schäper et al., we found arguments that support the improvement of gas exchanges after antibody therapy. At baseline two patients presented desaturation during exercise, after the initiation of anti-IL5 therapy both of them improved and showed no more desaturation at follow up CPET. Consistently with this, both of them experienced symptom improvement, gain of FEV1 and raise of capillary pO2 at rest and during exercise. Furthermore, 7 patients depleted their breathing reserve during baseline exercise, and all of them restored it to normal values after 3 months of anti-IL5 therapy.

Other indicators of a ventilatory efficiency improvement were the reduction of respiratory rate at the peak of exercise (from 36/min to 31/min, $p=0.058$) and gain of capillary pO2 at rest (from 72 to 80 mmHg, $p=0.004$). No differences were detected in terms of tidal volume during exercise.

To our knowledge, no previous studies ever analyzed gas exchanges and exercise capacity through CPET before and after the initiation of anti-IL5 therapy in severe asthma patients. A recent review by Boutou et al. [22] reported data about ventilation/perfusion inequality induced by physical exercise in asthmatic patients. The uneven ventilation and the ventilation/perfusion inequality could be explained by bronchoconstriction and airways inflammation, since arterial pO2 and A-aDO2 were negatively correlated to the increase of histamine concentration in sputum, as demonstrated by Haverkamp and colleagues [26]. Since gas exchanges and airflow limitation depend on the airways caliber and benralizumab and mepolizumab have anti-inflammatory effect on the respiratory tract and contribute to increase the FEV1, it is plausible that IL5 antibodies improve the ventilatory homogeneity and the respiratory efficiency [27,28]. In fact, in a recent analysis by Abdo et al., exercise limitation and poor symptoms control were strongly correlated and have been associated to small airway dysfunction in asthmatic patients [29].

The benefits of anti-inflammatory therapy on exercise capacity were previously described by Van der Meer et al. [9], who analyzed the response to corticosteroid treatment in a cohort of moderate-to-severe asthmatic patients. In their study, dynamic hyperinflation was significantly reduced by systemic glucocorticoid therapy, suggesting that anti-inflammatory treatment could improve exercise capacity and quality of life. Although in our population the dynamic hyperinflation was not detected in any patient in CPET, we found a reduction of RV from 139% to 124% (p=0.030) and RV/TLC from 47% to 41% (p=0.013) in 12 months after antibody start. In addition, as specific airway resistance dropped (127% to 87% (p=0.004)) and FEV1 and FVC increased, we suppose that mepolizumab and benralizumab decreased edema and inflammatory cell infiltration in the respiratory tract, resulting in enhanced airway caliber, control of small airways disfunction and alveolar recruitment [29-31].

MIP is an indicator of the respiratory muscle strength, that depends on the mechanical characteristic of the lungs, emphysema, hyperinflation and long term steroid therapy [32-34].

We did not find changes from baseline to follow up measurement in severe asthma patients under antibody therapy. Similarly, no differences were observed for P0.1 or P0.1/MIP values.

However, contrasting data are available about the impairment of muscular strength in asthmatic patients. A work by Ferreira Pereira and colleagues evaluated the 6 minute walking test, spirometry and measurement of respiratory muscle strength in 25 subjects with severe uncontrolled asthma [35] and found no changes even if oral corticosteroid use was taken into account. In contrast, De Bruin et al. demonstrated reduced MIP and greater diaphragm thickness in asthmatic patients compared to healthy controls [36], while no differences were detected in the strength of limb muscles. A significant improvement of respiratory muscle efficiency as demonstrated by Weiner and colleagues after administration of bronchodilator therapy [37]. These contradictions could be explained by the heterogeneous nature of asthma.

As oral corticosteroids could lead to muscular weakness and hypotrophy [38,39] we compared patients who were under steroid therapy at baseline with OCS-free patients. The MIP value was similar between the two groups, but patients treated with long-term OCS therapy had P0.1 values higher than patients without OCS treatment (median values respectively 0.47 vs 0.23 kPa, p=0.106, see *Table 3* and *Figure 2*). This difference was not significant but a trend was observed, and this finding is likely to be significant considering a larger sample size. Unfortunately, we could not conduct an analysis comparing P0.1 and MIP with different OCS dosage because of the little sample size, but it could be an interesting field for further studies.

Limitations

The major limitations of our study are the little sample size of the studied population and its monocentric nature. Therefore, it is not possible to compare different subgroups and there is no parallel nor control group. For this reason, the proposed work could be considered as a feasibility study or a pilot study.

In addition, in particular in real life, asthmatic patients have several comorbidities, that may influence the response to physical exertion [1,3,40].

Another limitation was related to the correlation between breathing reserve and FEV1. As MVV was derived from FEV1 (35xFEV1), BR improvement could be partly related to the increase of FEV1.

Our study could be furthermore implemented adding a control group composed of severe asthma patients not treated with antibody therapy, and performing CPET again at 6 and/or 12 months, to verify the effects of re-training and limb muscle strength and endurance.

CPET is very useful to analyze the pathophysiological mechanism of dyspnea and exercise limitation, but requires expensive instruments, time and employees. Severe asthma clinics could have little time and resources to regularly perform CPET in every patient.

Conclusion

This was the first study that evaluates CPET and respiratory muscle function after antibody therapy. These data give more insight in functional changes and help clinicians to understand the pathophysiological changes and improvements under therapy although its added value in everyday clinical practice remains questionable. The anti-inflammatory effect of anti-IL5 antibodies decreased edema and inflammatory cell infiltration in the respiratory tract, resulting in enhanced airway caliber and alveolar recruitment and improved ventilatory efficiency. For OCS long term therapy, we found some changes on P0.1 but its role and clinical value remain unclear.

Table 1. Baseline characteristics of the study population.

	Total (n 14)
Female sex	10 (71.4%)
Age, years	52 (47-61)
BMI	27.4 (24.5-29.3)
Obesity (BMI ≥ 30)	3 (21.4%)
Smoking status Never Former smokers	 2 (14.3%) 12 (85.7%)
Smoking pack years	6 (5-9)
Monoclonal therapy Mepolizumab Benralizumab	 7 (50.0%) 7 (50.0%)
High dose ICS + LABA therapy	14 (100.0%)
LAMA therapy	12 (85.7%)
Chronic use of OCS	7 (50.0%)
Leukotriene antagonist therapy	6 (42.9%)
Arterial Hypertension	5 (35.7%)
Allergic rhinitis	5 (35.7%)
Chronic rhinosinusitis with nasal polyps	2 (14.3%)
Chronic rhinosinusitis without nasal polyps	2 (14.3%)
Steroid-induced diabetes	2 (14.3%)
Heart failure	0 (0.0%)

BMI: Body Mass Index; ICS: inhaled corticosteroids; LABA: long acting beta agonists; LAMA: long acting muscarinic antagonists; OCS: oral corticosteroids.

All continuous variables are presented as median (IQR), all categorical variable as frequency (percentage).

Table 2. Functional parameter before and under antibody treatment

	Baseline	3 months	**p† (BL_3Mo)**	6 months	**p† (BL_6Mo)**	12 months	**p† (BL_12Mo)**	**pΔ (all)**
Pulmonary function tests								
FEV1 % predicted	56 (18)	80 (15)	**<0.001**	81 (14)	**0.001**	77 (17)	**0.002**	**0.009**
FVC % predicted	76 (21)	96 (8.4)	**0.003**	96 (10)	**0.004**	92 (14)	**0.041**	**0.021**
FEV1/FVC ratio	0.62 (0.16)	0.70 (0.13)	**0.015**	0.71 (0.13)	**0.009**	0.70 (0.11)	**0.010**	**0.009**
RV % predicted	139 (33)	124 (34)	**0.030**	127 (16)	**0.148**	128 (31)	**0.102**	**0.243**

TLC % predicted	100 (18)	104 (12)	**0.186**	104 (9)	**0.136**	103 (10)	**0.316**	**0.302**
RV/TLC, %	47 (10.2)	41 (9.7)	**0.013**	42 (6.1)	**0.030**	42 (8.4)	**0.052**	**0.127**
MEF25-75 % predicted	34 (16.8)	54 (25.9)	**0.005**	47 (23.8)	**0.028**	44 (22.4)	**0.075**	**0.053**
RAW % predicted	127 (54.8)	87 (34.7)	**0.004**	85 (31.4)	**0.005**	93 (21.7)	**0.022**	**0.043**
CPET								
W, watt	117 (38)	119 (29)	**0.801**					
V´O2 peak, ml/kg/min	19 (4.7)	19 (5.0)	**0.753**					
VE at rest, L/min	17 (3)	15 (3)	**0.035**					
VE peak, L/min	52 (16)	49 (11)	**0.272**					
BR peak, % pred	78 (17.4)	60 (14.3)	0.004					
Desaturation	2 (14.3%)	0 (0.0%)	-					
Respiratory work								
P0.1, kPa	0.29 (0.16)	0.35 (0.26)	**0.404**					
MIP, kPa median (IQR)	8.9 (5.9-12.7)	9.4 (4.7-10.4)	**0.799¥**					
P0.1/MIP (%)	3.9 (2.4)	4.0 (3.1)	**0.780**					

Other parameters								
ACT score	13 (4)	20 (5)	**0.003**	20 (5)	**0.028**	21 (5)	**0.008**	**0.108**
Eosinophil count, /µL	905 (1109)	35 (80)	**0.020**	NA	**-**	35 (79)	**0.001**	**0.016**
Capillary pO2 at rest, mmHg	72 (12)	80 (10)	**0.004**	79 (8)	**0.091**	84 (7)	**0.067**	**0.500**
Capillary pCO2 at rest, mmHg	36 (3)	38 (3)	**0.3**	37 (2)	**0.248**	37 (2)	**0.12**	**0.783**
Exacerbations number last year, median (IQR)	2 (1-4)					0 (0-2)	**0.012**	

† Pair-sample T test was applied for all variables where not otherwise indicated.

¥ Wilcoxon test

Δ Linear model for repeated measures (Wilk's Lambda)

All continuous variables are shown as mean (sd) where not otherwise indicated and all categorical variable as frequency (percentage).

FEV1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; RV: Residual Volume; TLC: Total Lung Capacity; MEF: Mean Expiratory Flow; RAW: Airway Resistance; CPET: cardiopulmonary exercise test; V´O2: oxygen consumption; VE: ventilation; BR: breathing reserve; P0.1: pressure generated during the first 0.1 second; MIP: Maximal Inspiratory Pressure; NA: Not available; IQR: interquartile range; ACT: Asthma Control Test; pO2: partial pressure of oxygen; pCO2: partial pressure of carbon dioxide.

Table 3. Comparison of inspiratory pressure values **<u>at baseline</u>** between patients under OCS vs patients without OCS treatment.

	OCS-free (n 7)	**Chronic OCS (n 7)**	**p**[+]
P0.1, kPa	0.23 (0.10-0.29)	0.47 (0.23-0.53)	0.106
MIP, kPa	9.7 (4.5-10.3)	9.3 (4.8-14.3)	0.792
P0.1/MIP (%)	2.5 (1.8-4.8)	5.0 (2.5-7.0)	0.247

All values are shown as median (interquartile range)

[+] Mann-Whitney U test was applied

OCS: oral corticosteroid; P0.1: pressure generated during the first 0.1 second; MIP: Maximal Inspiratory Pressure.

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Declarations

Ethics approval and consent to participate: All patients provided written informed consent to use their medical data and all retrospective analyses were performed with approval of the local institutional review board (9171_BO_K_2020).

Consent for publication: not applicable

Availability of data and materials: the datasets generated during and/or analyzed during the current study are available from the corresponding author upon individual and specific request. The use of individual data of patients outside specific personal consultation will not be permitted.

Declarations of interest: the authors declare that they have no competing interests

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Authors' contributions: Conceptualization, project administration: HS, ND, TW. Data collection: HS, EF, BF. Methodology, data analysis: EF, JF. All authors discussed the results and contributed to writing, review and editing. All authors read and approved the final manuscript.

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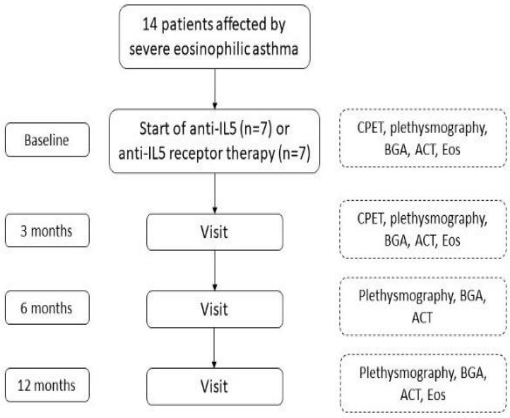
14 patients affected by severe eosinophilic asthma
Baseline
Start of anti-IL5 (n=7) or anti-IL5 receptor therapy (n=7)
CPET, plethysmography, BGA, ACT, Eos
3 months
Visit
CPET, plethysmography, BGA, ACT, Eos
6 months
Visit
Plethysmography, BGA, ACT
12 months
Visit
Plethysmography, BGA, ACT, Eos

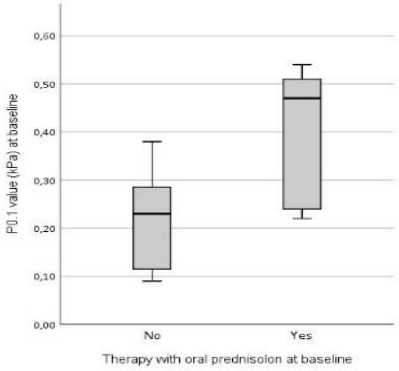
0,60
0,50
0,40
0,30
0,20
0,10
0,00
P0.1 value (kPa) at baseline
No
Yes
Therapy with oral prednisolon at baseline

Table S1. Comparison between CPET parameters recorded at baseline and 3 months after the initiation of antibody drugs.

	Baseline	**3 months**	**p†**
V´O2 peak, ml/kg/min	19 (4.7)	19 (5.0)	0.753
V´O2 peak, % pred	80 (17)	83 (16)	0.660
V´O2 at AT, ml/kg/min	14 (2.8)	13 (2.9)	0.405
V´O2 at AT, % pred	64 (19)	60 (11)	0.359
W peak, watt	117 (38)	119 (29)	0.801
W peak (% pred.)	76 (18)	78 (18)	0.889
VE at rest, L/min	17 (3)	15 (3)	0.035
VE peak, L/min	52 (16)	49 (11)	0.272
RR at rest, /min	22 (5)	19 (5)	0.092
RR at AT, /min	25 (8)	22 (4)	0.241
RR peak, /min	36 (10)	31 (6)	0.058
BR peak, %	78 (17.4)	60 (14.3)	0.004
BR peak ≥ 85%	7 (50.0%)	0 (0.0%)	-
O2 pulse peak, % pred	90 (24)	80 (26)	0.345
O2 pulse peak < 80%	5 (35.7%)	5 (35.7%)	-
pO2 peak, mmHg	93 (14)	90 (6)	0.655
Desaturation	2 (14.3%)	0 (0.0%)	-
VE/V´CO2 slope	24 (6.0)	25 (4.5)	0.963
VE/V´CO2 slope ≥ 35	1 (7.1%)	1 (7.1%)	-
Interpretation			
Normal test	2 (14.3%)	5 (35.7%)	
Deconditioning	6 (42.9%)	7 (50.0%)	
Cardiac limitation	3 (21.4%)	2 (14.3%)	
Ventilatory impairment	7 (50.0%)	0 (0.0%)	

† Pair-sample T test was applied for all variables. All continuous variables are shown as mean (sd).

AT: anaerobic threshold; peak: at the peak of exercise; % pred: percentage of the predicted value; V´O2: oxygen consumption; W: work load reached (Watt); VE: ventilation; RR: respiratory rate; BR: breathing reserve; pO2: partial pressure of oxygen;

Table S2. Comparison of inspiratory pressure values and lung function parameters recorded at baseline between patients under corticosteroid therapy versus OCS-free patients.

	OCS-free (n 7)	**Chronic OCS (n 7)**	**p®**
P0.1, kPa	0.23 (0.10-0.29)	0.47 (0.23-0.53)	0.106
MIP, kPa	9.7 (4.5-10.3)	9.3 (4.8-14.3)	0.792
P0.1/MIP (%)	2.5 (1.8-4.8)	5.0 (2.5-7.0)	0.247
FEV1, L	1.44 (1.13-1.96)	1.86 (1.34-1.99)	0.710
FEV1, % predicted	48 (38-81)	56 (51-63)	0.535
FVC, L	2.79 (1.87-3.68)	2.62 (1.86-3.90)	0.902
FVC, % predicted	79 (54-102)	78 (61-83)	0.996
RV, L	2.71 (2.10-3.00)	3.16 (1.78-3.37)	0.456
RV, % predicted	123 (116-139)	131 (127-175)	0.318
RAW, % predicted	129 (54-171)	117 (94-194)	0.710

® Mann-Whitney U test

All continuous variables are shown as median (IQR).

P0.1: pressure generated during the first 0.1 second; MIP: Maximal Inspiratory Pressure; FEV1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; RV: Residual Volume; RAW: Airway Resistance.