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Omalizumab treatment and exercise capacity in severe asthmatics — Results from a pilot study

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Summary
Background: In patients with moderate to severe allergic asthma, clinical effectiveness of omalizumab, an approved anti-IgE-reacting substance, is usually assessed by pulmonary function testing (PFT), symptom scores and physicians judgement.
Aims: We postulate that cardiopulmonary exercise testing (CPET) may provide an additional option to verify symptomatic changes in patients with allergic asthma.
Methods: Ten consecutive patients with allergic asthma were treated with omalizumab. Prior to and after 16 weeks of treatment all patients underwent PFT and symptom-limited CPET. Results were compared to 10 asthmatic controls without omalizumab medication. Symptoms were assessed according to investigators judgement (IGETE).
Results: All 20 patients showed a significantly impaired exercise capacity at baseline [peak oxygen uptake (VO_2) 71 ± 16% predicted]. In patients with omalizumab, peakVO_2 increased from 13.8 (8.4–21.4) to 16.8 (11.2–23.9) ml/kg/min ($p < 0.05$), VO_2 at anaerobic threshold increased by 22% [9.8 (3.3–15.2) to 12.3 (6.7–14.4) ml/kg/min ($p < 0.05$)]. There was no improvement in the controls. The increase in VO_2 was significantly correlated to the improvement in symptoms. All patients revealed dynamic hyperinflation under exercise with a decreasing extent with omalizumab treatment.

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Conclusion: This study suggests that CPET may provide additional and useful tools to assess and verify the individual clinical response to omalizumab treatment. An improvement in exercise capacity can reliably mirror changes in quality of life and IGETE. Patients with omalizumab experience significant improvements in their initially impaired exercise capacity. CPET can be safely accomplished in patients with severe asthma.

Introduction

Omalizumab, an established and approved anti-immunoglobulin-E (anti-IgE) reacting substance, has been shown to be effective in the treatment of patients with moderate to severe allergic asthma.[1–6] Omalizumab related treatment success has been shown by improved quality of life and symptom scores, less frequent exacerbations, reduced need of anti-inflammatory as well as rescue medications and improved lung function.[1–6] Furthermore, a strong evidence of anti-inflammatory potencies of anti-IgE exists.[7,8] To what extent all these factors may influence exercise capacity in this patient population has not been studied yet.

Cardiopulmonary exercise testing (CPET) provides the possibility to reliably quantify exercise capacity in diseased and healthy subjects by measuring oxygen uptake at anaerobic threshold (VO_2@AT) and peak exercise (peakVO_2).[9] Furthermore, exercise capacity and ventilatory efficiency — usually expressed as the regression of ventilation to carbon dioxide output (VE vs. VCO_2 slope) — has been shown to be well correlated to dyspnoea and survival in patients with cardiac and pulmonary diseases.[10–13] In patients with impaired lung function due to airflow limitation, exercise induced pulmonary hyperinflation is well correlated to dyspnoea and exercise capacity.[14,15] Both, exercise capacity and dynamic hyperinflation has been shown to be potentially improved by bronchodilators.[16]

The individual effectiveness of omalizumab treatment is usually assessed by physician's judgment based on a clinical evaluation since objective laboratory and technical examinations have not been shown any superiority. The major aim of this study was to investigate the potential impact of CPET describing the treatment effects of omalizumab. We postulate that improvements reported by the patients under omalizumab may be verified and quantified by gas exchange analysis within a symptom limited incremental exercise test.

Methods

Study population and treatment protocol

Ten consecutive prospectively assigned adults with severe allergic asthma due to perennial allergens and positive skin prick test underwent pulmonary function testing (PFT) and CPET prior to and after 16 weeks of omalizumab treatment. Indication for omalizumab therapy was given by insufficient symptom control under conventional asthma therapy and patients agreement for additional omalizumab treatment following the manufacturers recommendations. CPET and PFT were conducted as integrative parts of their regular visits in an outpatient clinic for asthma and allergies of the UniversityHospital. Omalizumab was dosed according manufacturers' recommendations (Novartis Pharma GmbH®, Germany) in an open labelled fashion. The results were compared to 10 consecutive controls with severe asthma, but without omalizumab treatment. Severe asthma was defined by a predicted forced expiratory volume in 1 s (FEV_1) <80%, day or night time asthma symptoms more than twice a week and documented frequent asthma exacerbations, requiring systemic corticosteroids or emergency services/hospitalization, during the year prior to initiation of omalizumab.

All 20 patients received at least high dose inhalative glucocorticosteroids eqivalent to 1000 μg Fluticasone propionate per day and inhalative long-acting inhaled β_2-agonists at least 4 weeks prior inclusion to the study. Subjects with known cardiac, muscular or other than asthmatic pulmonary diseases were excluded from the study. Investigator ratings of global evaluation of treatment effectiveness (IGETE) are a tool meanwhile established for the description of treatment success under omalizumab therapy.[1,17] We categorized IGETE using a scoring system: 2 = significant improvement, 1 = slight improvement, 0 = no change.

All patients gave written informed consent. The study conformed to the principles of the Declaration of Helsinki as reflected by an a priori approval of the local Ethics Committee.

Exercise testing and gas exchange variables

Immediately prior to CPET, each subject underwent a PFT including spirometry and body plethysmography according to current recommendations.[18] Each subject performed symptom-limited CPET on a bicycle with ramp wise exercise increment of 5 Watts per minute. Details of the protocol and the gas exchange analysis have been published elsewhere.[19] In the absence of chest pain, ECG abnormalities, complex arrhythmias or critical blood pressure changes, all tests were performed symptom-limited (volitional exertion, dyspnoea or fatigue). Prior to CPET, all patients were encouraged to reach maximal exhaustion. All tests were performed according to current guidelines for CPET[20,21] with continuous monitoring of gas exchange, 12-lead ECG, blood pressure and oxygen saturation. Values for oxygen uptake have been compared to currently published reference values.[22]

Statistical analysis

Values are given as median, confidence intervals (CI) and ranges as outlined. Between-group comparisons were made

using the Mann–Whitney *U* test. A 2-tailed *P*-value below 0.05 was considered statistically significant.

For the present pilot study it was planed to include 10 patients and 10 controls. Primary objective was, to investigate whether patients under omalizumab treatment develop an improvement of oxygen uptake (VO_2) as an objective, verifiable parameter of exercise capacity.

All statistical analyses were performed with SPSS software, version 17.0 (SPSS GmbH Software, Munich, Germany).

Results

All patients treated with omalizumab completed the 16 weeks period without interruptions and complications. All subjects successfully performed CPET without complications or premature terminations. Besides omalizumab initiation in the treatment group and rescue medications all anti-asthmatic medications remained unchanged. Neither patients with omalizumab nor controls experienced severe exacerbation or hospitalisations within the 16 weeks of the study period. Two of 10 omalizumab treated patients revealed no symptomatic changes (IGETE 0), 4/10 slight improvements (IGETE 1), and 4/10 significant improvements (IGETE 2).

PFT and CPET results at baseline and after 16 weeks are given in Table 1. Both groups showed a significantly impaired exercise capacity baseline: controls 73% (range 57–83) predicted peakVO_2; treatment group 63% (44–77) predicted peakVO_2; follow up: 74 (56–82) vs. 70 (56–80) %; $p < 0.05$ for in between and follow up comparisons of the omalizumab group). Median peak expiratory exchange rate achieved 1.17 (range 0.95–1.35) in the treatment group (follow up test 1.19; 0.96–1.28 n.s.) and 1.15 (range 0.99–1.25) in controls (follow up 1.17; 1.01–1.24 n.s.). Omalizumab treated patients revealed a significant increase in forced expiratory volume in 1 s (FEV_1) and peakVO_2. Ventilatory efficiency quantified as VE vs. VCO_2 slope was not impaired in both groups. Dynamic flow volume loops were attainable in 7/10 subjects in the treatment group and in 7/10 controls. At baseline and after 16 weeks, 6/7 control subjects and 7/7 subjects in the omalizumab group revealed dynamic hyperinflation with decreasing inspiratory capacities at peak exercise levels. Neither omalizumab treated nor control subjects revealed a peak tidal volume to inspiratory capacity ratio (Vt/IC) above 0.9 at baseline and follow up. The degree of hyperinflation decreased in the treatment group and remained unchanged in controls. Individual changes in peakVO_2 and VO_2@AT are given in Figs. 1 and 2. Changes in peakVO_2 in relation to the clinical response (IGETE) are given in Fig. 3.

Discussion

Patients with severe allergic asthma treated with omalizumab reveal a significantly improved exercise capacity.

Table 1 Patient characteristics.

	Omalizumab ($n = 10$)		Controls ($n = 10$)	
	Baseline	Follow up	Baseline	Follow up
Sex [female/male]	7/3		6/4	
Age [years]	54.5 (29–63)		56 (25–69)	
IgE [I.U./ml]	240 (33–684)		382 (2.8–900)	
Pulmonary function testing				
FEV_1 [l]	1.215 (0.35–2.61)	1.55** (0.55–2.64)	1.46 (0.93–2.36)	1.58 (0.96–2.38)
R_{tot} [kPa*s/l]	0.625 (0.34–1.4)	0.49 (0.3–1.03)	0.57 (0.25–0.73)	0.395 (0.2–0.58)
FVC [l]	2.26 (1.08–3.83)	2.42 (1.05–3.93)	2.9 (2.72–3.33)	2.935 (2.78–3.2)
ITGV [l]	3.99 (2.446.14)	3.57*$^{+}$ (2.2–6.06)	3.45 (2.17–5.03)	3.69 (2.42–5.21)
TLC [l]	5.84 (3.67–7.53)	5.44 (3.18–7.47)	5.65 (4.59–7.2)	5.895 (4.33–7.56)
Cardiopulmonary exercise testing				
VO_2				
peak [l/min]	1.1 (0.58–1.86)	1.275* (0.72–2.09)	1.38 (0.87–2.09)	1.34 (1.11–1.45)
peak [ml/kg/min]	13.8 (8.5–21.6)	16.8* (11.2–23.9)	19.4 (13.8–27.1)	18.8 (13.8–27.8)
AT [ml/kg/min]	9.83 (3.3–15.2)	12.3* (6.7–14.4)	10.5 (6.2–19.5)	11.1 (7.6–14.7)
VE vs. VCO_2slope	25.7 (22–34)	25.1 (23–33)	26.1 (22–34)	26.5 (20–33)
peakVE [l]	33.9 (17.5–59.0)	37.325* (21.3–68.4)	47.435 (33.8–68.3)	49.16 (33.7–73.3)
peakVt [l]	1.3 (0.53–1.98)	1.355 (0.62–1.9)	1.605 (1.28–1.97)	1.53 (1.19–2.14)
peakBF [1/min]	31.5 (26–35)	33 (23–37)	33 (20–36)	32 (24–36)
peak breathing reserve [%]	75 (62–82)	76 (66–84)	78 (50–93)	78 (68–91)
peakVt/IC	0.68 (0.53–0.76)	0.71 (0.51–0.8)	0.67 (0.55–0.81)	0.68 (0.57–0.83)

Patient characteristics at baseline and week 16 (follow up) given as median and ranges. * for $p < 0.05$, ** for $p < 0.01$ vs. baseline; $^{+}$ for $p < 0.05$ omalizumab vs. controls. *n* – numbers; FEV_1 – forced expiratory volume in 1 s; R_{tot} – airway resistance; FVC – forced vital capacity; ITGV – intrathoracic gas volume measured by body plethysmography; TLC – total lung capacity, VO_2 – oxygen uptake; AT – anaerobic threshold; VCO_2 – carbon dioxide output; VE vs. VCO_2 slope – ventilatory efficiency quantified as slope of the regression of VE to VCO_2; VE – minute ventilation; Vt – tidal volume; BF – breathing frequency. Breathing reserve assessed as 100–(peakVE/$FEV_1 \times 41$) $\times$ 100 [26].

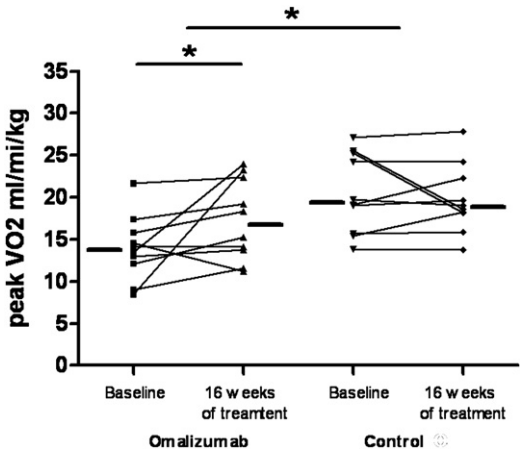

Figure 1 Peak oxygen uptake (VO_2) at baseline and follow up of treated subjects and controls. * for $p < 0.05$.

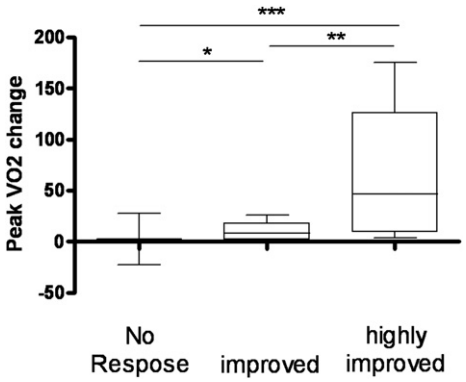

Figure 3 Percent changes in peak oxygen uptake (peakVO_2) from baseline to follow up in correlation to clinical response. No response — IGETE 0; improved — IGETE 1; highly improved — IGETE 2. * for $p < 0.05$; ** for $p < 0.01$; *** for $p < 0.001$.

Oxygen uptake at anaerobic threshold and peak exercise increased remarkably compared to baseline and compared to controls. The increase in oxygen uptake mirrored the improvement in symptoms as investigated by IGETE. The increase in exercise capacity was accompanied by a decrease in dynamic hyperinflation.

To the best of our knowledge these are the first data evaluating the potencies of CPET to reliably assess a medical treatment effect in patients suffering on asthma. Treatment success due to omalizumab has been described by improved symptom scores, reduced exacerbations, improved lung function and a decreased need of anti-asthmatic medications.[1—6] However, all these endpoints may be biased by investigators and patients. Thus, we assume that parameters assessed by CPET such as peakVO_2 and VO_2@AT provide additional reliable options to evaluate treatment success and to verify changes in symptoms in this patient population. One may criticize that peak exercise capacity is dependent on patients' motivation too. However, the increase in peakVO_2 was accompanied by a parallel increase in VO_2@AT — a motivation independent parameter.[9,23]

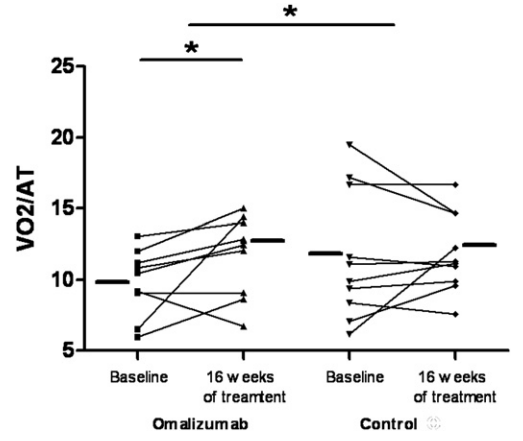

Figure 2 Oxygen uptake at anaerobic threshold (VO_2/AT) at baseline and follow up of treated subjects and controls. * for $p < 0.05$.

Patients with asthma included in this study show a significantly impaired exercise capacity in relation to healthy controls.[22] In general, exercise capacity is depending on multiple confounders influencing pulmonary, cardiac, circulatory and muscular function or dysfunction.[9] Whereas exercise capacity in patients with heart diseases is usually deteriorated by cardiac dysfunction and ventilator inefficiency (VE vs. VCO_2 slope),[12,13,24] exercise-limiting factors in pulmonary diseases are heterogeneous.[11,15,16,25] The mechanism of dynamic hyperinflation resulting in decreasing attainable lung volumes under exercise has been well described in patients suffering on airflow limitation due to chronic obstructive pulmonary diseases (COPD).[14,15] In COPD patients, dynamic hyperinflation accounts for dyspnoea and exercise intolerance.[14,15] To what extent this mechanism impacts exercise capacity in patients with allergic asthma has not been described yet. Except one control all investigated subjects in our study shared the characteristics of dynamic hyperinflation with COPD patients. Furthermore, the extent of dynamic hyperinflation decreased with omalizumab, corresponding to an improvement in symptoms and exercise capacity. However, none of the included patients showed ventilatory constrains feasible to be of exercise limiting quantity since the Vt/IC ration remained below 0.9. However, this study is neither powered nor designed to completely clarify exercise-limiting factors in asthma. Thus, it is limited in giving causal explanations about complex cohesions of exercise and pulmonary function physiology remains unresolved to some extent. The mechanisms leading to the improved exercise capacity under omalizumab treatment and its associations with traditional methods such as FEV_1 has to be investigated in future studies.

This study may further be criticized for not being blinded and randomized. We understand our results as an initial attempt to describe a possible new method to evaluate treatment success due to omalizumab and possibly due to other anti-asthmatic medications. Furthermore, as in several studies investigating omalizumab we applied IGETE[1,17] to quantify treatment response in comparison to CPET. Since IGETE may be influenced by the investigators judgement we cannot rule out some bias. For future studies

additional questionnaires to assess patients symptoms may help to reliably measure treatment effects.

Finally, it has to be outlined that in patients with severe asthma CPET can easily be accomplished and is safe.

Conclusion

This study suggests that CPET may provide additional and useful tools to assess and verify the individual clinical response to omalizumab treatment. An improvement in exercise capacity can reliably mirror changes in quality of life and IGETE. Patients with omalizumab experience significant improvements in their initially impaired exercise capacity. CPET can be safely accomplished in patients with severe asthma.

All authors' state to have significantly contributed to the conception and design as well as the analysis and interpretation of data, drafting of the manuscript and revising it critically for important intellectual content; and the final approval of the manuscript submitted.

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Disclosures

All authors state to have nothing to disclose.

Conflict of interest

None.

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