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Long-term effect of home-based pulmonary rehabilitation in severe asthma

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ABSTRACT

Introduction: Home-based pulmonary rehabilitation (PR) has demonstrated its effectiveness amongst patients with chronic obstructive pulmonary disease (COPD) but has never been investigated in severe asthma.
Methods: In a retrospective study, we included 28 patients with severe asthma (61.5 ± 16.2 years, FEV1: 51.4 ± 17.3%) and 164 matched COPD patients (64.3 ± 11.6 years, FEV1: 47.7 ± 15.5%) who had completed a home-based PR program and pursued at least 12 months of follow-up. The number of steps performed during a 6-min stepper test (6MST), the Hospital Anxiety and Depression (HAD) scores, and the Visual Simplified Respiratory Questionnaire score (VSRQ) were compared between baseline, the post-PR period (post-PR) and after 12 months of follow-up (M12) within each group. The evolution of the 6MST, HAD and VSRQ values between baseline, post-PR and M12 was compared between severe asthma and COPD patients.
Results: In the severe asthma group, the 6MST was higher post-PR (504 ± 150, $p = 0.043$) and at M12 (538 ± 163, $p = 0.016$) compared with baseline (450 ± 148). The VSRQ score was higher at M12 (39.0 ± 18.6, $p = 0.049$) but not post-PR (38.7 ± 15.8, $p = 0.119$) in comparison with baseline (32.2 ± 12.4). There was no difference in the HAD scores between baseline, post-PR and M12. PR outcome was not significantly different between severe asthma and COPD patients at short and long term ($p > 0.05$).
Conclusion: In severe asthma, home-based PR is associated with improved exercise tolerance and quality of life on a long-term basis but does not modify anxiety and depression.

1. Introduction

Around 5% of people with asthma have severe asthma, which is defined by a resistance to high-dose inhaled corticosteroids combined with a second "controller" or even with oral corticosteroids [1]. Despite extensive therapy, patients with severe asthma have repeated or permanent symptoms, present with frequent exacerbations requiring emergency care or hospitalisations [2], and develop multiple complications due to oral corticosteroids such as obesity, diabetes and heart diseases [3]. Severe asthma is associated with disabling dyspnoea, exercise intolerance [4,5] and reduction in physical activity [6] leading to a major alteration of quality of life [2]. Although biotherapies have significantly improved the management of patients with severe asthma, they are beneficial only in Type 2 phenotypes and their effect on exercise tolerance and physical activity remains unknown. Therefore, respiratory disability of patients with severe asthma currently remains beyond any therapeutic resource.

Pulmonary rehabilitation (PR) is a global management program dedicated to patients suffering from chronic respiratory diseases. This program includes exercise training, resumption of physical activities of daily living, therapeutic education, and psychological, social and motivational support. In chronic obstructive pulmonary disease (COPD), PR effectiveness has been extensively demonstrated on the rate of exacerbations, dyspnoea severity, quality of life, anxiety and depression [7], regardless of being performed in a PR centre or at home [8,9]. In asthma of all severity, PR is associated with short- and long-term improvement in asthma symptom control and quality of life. On a short-term basis, PR was also shown to be associated with decreased dyspnea perception, anxiety and depression, and increased exercise tolerance [10,11]. However, there are only few data in severe asthma and none

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concerns long-term effects or home-based programs.

We hypothesized that home-based PR could improve exercise tolerance, quality of life, anxiety and depression of patients with severe asthma, similarly to COPD patients. We built this study to assess the short- and long-term effect of home-based PR on exercise tolerance, quality of life, anxiety and depression in patients with severe asthma in comparison to patients with COPD.

2. Methods

2.1. Patients

In this single-centre retrospective study, all patients with severe asthma referred for a home-based PR from January 2014 to June 2016 were assessed for inclusion in the study. The diagnosis of severe asthma was hold by the referring chest physician according to the criteria defined by the ATS/ERS guidelines [1,12]. The choice to perform PR at home rather than in a PR centre was based on the patient's personal preference and/or the absence of a local centre. Exclusion criteria were dementia or uncontrolled psychiatric illness, neurological sequelae or bone and joint disease preventing physical activity, hyperventilation syndrome or uncontrolled comorbidity and pregnant or breastfeeding women. Patients receiving oxygen therapy and/or non-invasive ventilation and/or with stable comorbidities could be included in the study.

The control group included COPD patients who had performed a similar home-based PR program during the same period. In order to be able to draw comparisons between the groups, COPD patients were matched according to height < 178 cm (maximum value in the severe asthma group), forced expiratory volume in 1 s (FEV_1) > 17%, forced vital capacity (FVC) > 35%, FEV_1/FVC > 35%, diffusing capacity of the lung for carbon monoxide (DLco) > 35% (minimum values in the severe asthma group), and total lung capacity (TLC) between 75 and 160% (extreme values in the severe asthma group).

Socio-demographic, clinical and functional data were collected prospectively and entered in a computerised file (Care Itou®) registered at the *CNIL* (French National Commission for information technology and civil liberties) (under No. 1523095v0) in the framework of the cohort follow-up. All the patients signed a written consent regarding the use of their personal data. This study was approved by the *Comité d'Evaluation des Protocoles de Recherche Observationnelle* (Observational research protocol evaluation committee) of the *Société de Pneumologie de Langue Française* (French Language Society of Pneumology) (CEPRO 2017–007).

2.2. Home-based pulmonary rehabilitation

The home-based PR program started with an educational diagnosis and a motivational interview. As described previously [13], home-based PR included a 1.5 h home visit once a week for 8 weeks, comprising exercise training and resumption of physical activities, therapeutic education and "self-management". Each session was conducted under the direct supervision of a team member, when patients continued physical exercise on their own on the other days of the week, according to a personalised and negotiated action plan. Assessment of exercise tolerance, anxiety, depression and quality of life was performed at home before, after the program (post-PR) and after 12 months of follow-up (M12 post-PR). During this evaluation, the difficulties experienced by the patient and his family were analysed, the results were showcased and motivational reinforcement was performed for both the patient and the spouse or carer who attended regularly the sessions. Healthcare professionals involved in the patient's care (general practitioner, physiotherapist, pharmacist, nurse) were informed about the home-based PR and were invited to participate in the program while continuing usual care throughout the program, without planning any other additional visit.

2.2.1. Therapeutic patient education

Depending on the patient's needs, the therapeutic education program approached the following topics: asthma, comorbidities, long-term and asthma attack treatments, prevention and recognition of exacerbations, the importance of physical activities, stress management, balanced diet, smoking cessation, self-image and self-esteem. Therapeutic education sessions were performed individually during each home visit, in most cases in the presence of the spouse or carer, by using methods and tools adapted to the patients and in relation to the addressed topic.

2.2.2. Psychosocial support and self-management

Particular attention was paid to the psychological, behavioural and motivational approach, to the motivational stages for the different health behaviours, to the stage of acceptance of the disease in the framework of a global management which nature is "self-management" [14]. Short, medium and long-term patient's personal projects were motivation levers to maintain these changes over time.

2.2.3. Exercise conditioning and adapted physical activities

The target heart rate (HR) for exercise training was tailored on the 6MST and calculated as 60% of the HR reserve, defined as $(HR_{peak} - HR_{rest}) * 0.6 + HR_{rest}$ with HR_{peak} being peak HR during the 6MST and HR_{rest} the resting HR [15]. The value was always checked by a comparison with the peak HR value from a 6-min walk test (6MWT) or the ventilatory threshold HR from a cardiopulmonary exercise test. Exercise training program included endurance exercises on cycle ergometer (Domyos VM 200©, Decathlon, France), at the target HR, in line with the patient's personal physical capabilities, initially on the basis of 10-min sequences (sometimes shorter sequences for patients with the most severe form of the disease) at least 5 days per week. Exercise intensity was gradually increased according to the target HR. The patient concurrently learnt how to recognise the target intensity of the exercise depending on the intensity of the dyspnoea (corresponding to a score between 3 and 4 on the 0 to 10 Borg scale) [16] or on the rating of perceived exertion (corresponding to a score between 11 and 13 on the 6 to 20 Borg scale) [17]. Some activities of daily living such as walking outdoors, climbing stairs, doing the housework, gardening, at the dyspnoea threshold were immediately integrated during the program. A personalised action plan was stated with the patient in order to keep performing his/her exercises during the other days of the week. Exercise training included three daily upper and lower limb muscle strengthening exercises for 10–15 min per day, using weights and dumbbells (0.5 or 1 kg) and/or elastic bands (Elastiband®). Each exercise comprised a series of 10 repeated movements. A 1-min recovery period was observed between exercises. Finally, warming-up and stretching exercises were also recommended, together with balance exercises whenever necessary.

Throughout the program, the team emphasised the need to keep performing physical activities integrated into daily living and chosen by the patient according to his/her preferences and local possibilities, on a long-term basis.

2.3. Outcomes

The primary outcome was the change after RR compared to baseline in exercise tolerance, assessed by the number of steps performed during a 6-min stepper test (6MST) (Stepper Athlitech©, Go Sport) [18]. The minimal clinically important difference (MCID) was 40 steps [19].

Secondary outcomes were the change after RR compared to baseline in anxiety, depression and health-related quality of life. Anxiety and depression were assessed by the Hospital Anxiety Depression scale (HADs) which consists of 7 questions on anxiety and 7 questions on depression [20]. The MCID was 1.5 points [21]. The quality of life was assessed by the Visual Simplified Respiratory Questionnaire (VSRQ) which comprises 8 visual analogue scales from 0 to 10, 0 corresponding

to the most important impact for the patient. The MCID was 3.4 points [22].

2.4. Severe adverse event

The PR agreement handed over to the patient before PR included a severe adverse event protocol. A severe adverse event was defined as death, hospitalisation or an emergency care requirement for heart or orthopaedic disease during the 8 weeks of the PR program. The patient and/or the therapist could declare the occurrence of severe adverse events. Patients were asked to interrupt all physical activities in case of any abnormal sensation, especially chest or joint pain and to contact both the rehabilitation team and the attending general practitioner.

2.5. Statistical analysis

Data are expressed as mean and standard deviation. Normal Gaussian distributions were verified by the Shapiro-Wilk test and the equality of variances by the Levene's test.

Numerical variables at baseline were compared between groups (severe asthma vs COPD) using a Student *t*-test or a Mann-Whitney *U* test and qualitative variables were compared using a Chi^2 test. Within each group (severe asthma and COPD), variables were compared between baseline, post-PR and at 12 months of follow-up (M1) using a general linear model for repeated measures, in which the number of steps performed during the 6MST, HAD and VSRQ scores were entered as independent variables. The sphericity was checked by the Mauchley test and, when it was not met, the significance of *F*-ratios was adjusted according to the Greenhouse-Geisser procedure or the Huyn-Feldt procedure. When significant differences were obtained, a Bonferroni *post-hoc* test was conducted. The magnitude of the difference was assessed by the effect size (ES). The scale proposed by Cohen [23] was used for interpretation. The magnitude of the difference was considered to be trivial ($ES < 0.2$), small ($0.2 \leq ES < 0.5$), moderate ($0.5 \leq ES < 0.8$), and large ($ES \geq 0.8$). In order to investigate a possible group effect, the differences between post-PR and baseline values and M1 and baseline values were compared between groups using Student *t*-test or Mann-Withney test. Statistical significance was set at $p < 0.05$. All analyses were performed with the Statistical Package for the Social Sciences (release 18.0, Chicago, IL, USA).

3. Results

3.1. Patients

From January 2014 to June 2016, 32 patients with severe asthma were referred for home-based PR. Amongst them, one patient refused to perform home-based PR due to a “lack of motivation” and three other patients were not included in the study due to hyperventilation syndrome. Amongst the 28 analysed patients, 2 did not complete the program (1 went on holyday, 1 suffered from widespread “arthritis” pain) and 2 other were not assessed at 12 months (1 refused the follow-up and the other one refused to perform the tests). During the same period, 298 patients with COPD were referred for home-based PR. Amongst them, we selected a population that was homogeneous to the population with severe asthma. Eventually, 164 patients with COPD were included in the study, 156 completed their PR program and 127 had an assessment at M12 (Fig. 1). Patients’ characteristics are summarised in Table 1. There were more women and more non-smokers in the group of patients with severe asthma and the FVC was higher than in the COPD group (Table 1). There was no difference between the 2 groups regarding the proportion of patients with 3 or more cardiovascular, metabolic, rheumatological or anxio-depressive comorbidities. A greater number of patients with severe asthma were treated with fixed drug combinations consisting of a long-acting beta-2 agonist and an inhaled corticosteroid (LABA/ICS), short-acting bronchodilators and oral corticosteroids and a smaller number had long-acting anticholinergic bronchodilators. Four patients with severe asthma were receiving a biotherapy. At baseline, there was no statistically significant difference between patients with COPD and patients with severe asthma regarding the number of steps performed during the 6MST as well as the VSRQ and anxiety and depression scores.

3.2. Short and long-term effects of PR

In the group of patients with severe asthma, the number of steps performed during the 6MST was significantly higher after PR than at baseline either in the short ($ES = +0.35$) or long term ($ES = +0.54$). Regarding the quality of life score, there was no statistically significant change post-PR (38.7 ± 15.8 vs 32.2 ± 12.4; $p = 0.119$) but it improved significantly at M12 post-PR ($ES = +0.42$) in comparison with baseline. However, there was no statistically significant change in the anxiety and depression scores neither post-PR nor at M12 post-PR ($p = 0.292$ and 0.235, respectively). In the COPD group, all parameters improved significantly post-PR and at M12 post-PR ($p < 0.001$) (Table 2).

Comparing the groups of patients with severe asthma and COPD, there was no statistically significant difference between groups in the evolution of the number of steps performed during the 6MST, VSRQ or anxiety and depression scores neither post-PR nor at M12 post-PR ($p > 0.05$) (Table 3).

3.3. Safety

No severe adverse event due to home-based PR was reported during the PR program in both groups of patients.

4. Discussion

This real-life study enabled us to assess the outcome of a home-based PR program on exercise tolerance, quality of life, anxiety and depression in severe asthma. Our results have demonstrated that home-based PR: 1) significantly improved long-term exercise tolerance and quality of life of patients with severe asthma, 2) similarly to COPD patients matched on pulmonary function but, 3) unlike COPD patients, was not associated with improvement in anxiety and depression.

Patients with severe asthma included in our study showed impaired exercise tolerance at a level similar to the one previously reported in severe COPD [18]. This is consistent with previous studies that reported a decrease in the distance walked during a 6MWT in patients with severe asthma in comparison with healthy subjects (499 vs 616 m) [6] and mild to moderate asthmatic patients (462 vs 608 m) [24] as well as a decrease in the peak oxygen uptake (VO_2 peak) ranging from 44 to 83% of the predicted value [4].

Amongst patients with severe asthma, our results have demonstrated a short-term improvement in exercise tolerance after PR confirmed by an increased number of steps performed during the 6MST of +87 steps in average, being twice the MCID (40 steps). These results concur with those of a non-controlled study that reported an improvement in the distance performed during the 6MWT of +33 m and of 10% in the VO_2peak after an outpatient PR program completed at home and at the physiotherapist office composed of 36 sessions including monitored adapted physical activities in group [25]. A comparative study with COPD also demonstrated an increase in the median endurance time of 378 s after an outpatient PR program composed of 20–30 sessions at the physiotherapist practice [26]. Additional studies conducted in asthmatics of various degrees of severity also reported an increase in the distance walked during a 6MWT [10,11]. Our study is the first to investigate the long-term effect of a home-based PR program on exercise tolerance in severe asthma, as defined by the ERS/ATS and GINA statements [1,12]. Our results showed that exercise tolerance improvement is maintained on a long-term basis after PR along with an

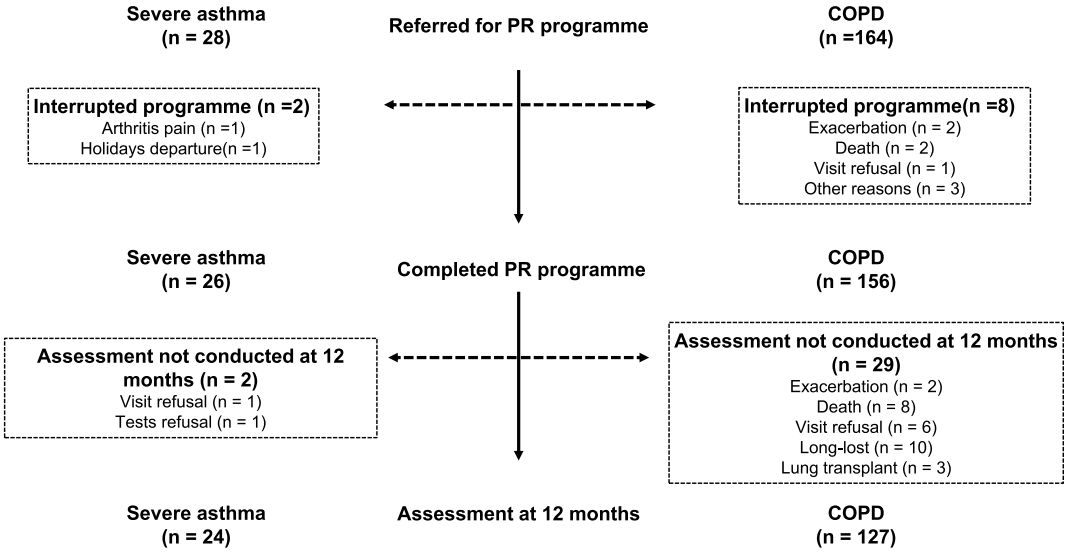

Fig. 1. Flow chart.

Table 1
Baseline characteristics of the patients.

	Severe asthma (n = 28)	COPD (n = 164)	p
Socio-demographic data			
Age, years	61.5 ± 16.2	64.3 ± 11.6	0.398
Women, n (%)	22 (78.6)	76 (46.3)	0.002
BMI, kg/m^2	29.6 ± 6.5	28.7 ± 8.1	0.901
Tobacco, n (%)			< 0.001
Non-smokers, n (%)	17 (60.7)	25 (15.2)	< 0.001
Ex-smokers, n (%)	9 (32.1)	114 (69.5)	< 0.001
Smokers, n (%)	2 (7.1)	14 (8.5)	1.000
Missing data, n (%)	0 (0)	11 (6.7)	0.372
≥3 comorbidities, n (%)	24 (85.7)	133 (81.1)	0.279
Treatment			
Combined LABA-ICS, n (%)	20 (82.1)	73 (44.5)	0.013
ICS, n (%)	5 (17.8)	26 (15.8)	0.784
LABA, n (%)	11 (39.3)	63 (38.4)	0.949
LAMA, n (%)	8 (28.6)	112 (68.3)	< 0.001
SABA, n (%)	28 (100)	81 (49,4)	< 0.001
Oral corticosteroids, n (%)	10 (35.7)	29 (17.7)	0.030
Montelukast, n (%)	10 (35.7)	0 (0)	< 0.001
Omalizumab, n (%)	2 (7.1)	0 (0)	0.021
Mepolizumab, n (%)	2 (7.1)	0 (0)	0.021
LTOT, n (%)	7 (25)	50 (30.5)	0.544
NIV, n (%)	5 (17.9)	41 (25)	0.404
CPAP, n (%)	3 (10.7)	19 (11.6)	1.000
Pulmonary **function test**			
FEV1 (% of the predicted value)	51.4 ± 17.3	47.7 ± 15.5	0.236
FVC (% of the predicted value)	81.4 ± 21.8	71.1 ± 18.1	0.026
FEV1/FVC (%)	59.9 ± 14.0	56.8 ± 9.9	0.376

6MST: 6-min stepper test; FVC: forced vital capacity, HAD: Hospital Anxiety Depression scale (-A: anxiety, -D: depression), ICS: inhaled corticosteroids, BMI: body mass index, LABA: long acting beta 2 agonists, LAMA: long acting muscarinic agonists, LTOT: long-term oxygen therapy, CPAP: continuous positive airway pressure, SABA: short acting beta 2 agonists, 6MST: 6-min stepper test, FEV1: forced expiratory volume in 1 s, NIV: non-invasive ventilation, VSRQ: visual simplified respiratory questionnaire.

average increase in the number of steps performed during the 6MST of +56 steps (MCID: 40 steps) at 12 months post-PR.

Contradictory results have been reported about PR outcome on the quality of life of patients with severe asthma. Bellocq et al. reported a major improvement in the Saint George's respiratory questionnaire score at the immediately after outpatient PR (−14.0 [-17.7 to −2.0] points) [26]. This was not found by Renolleau-Courtois et al. who used the Medical Outcome Study Short Form 36 (SF36) health survey questionnaire [25] that is probably less reactive to post-intervention changes than a specific pulmonary questionnaire. In addition, studies conducted in asthmatics of various degrees of severity showed PR to be associated with short- and long-term improved quality of life, in particular in uncontrolled asthmatics [10,11]. Two meta-analyses consistently found an association between physical training and quality of life improvement in asthmatic patients [27,28]). In our study, by using the VSRQ questionnaire that is specific to pulmonary diseases, we have demonstrated a long-term improvement in the quality of life of +6.8 ± 11.9 points exceeding the MCID, but not in the short-term (+8.8 ± 13.8 points), probably due to a lack of statistical power.

Contrary to the Bellocq et al. study, our results did not reveal any improvement in anxiety and depression post-PR in a group of patients with severe asthma mainly composed of women, mostly obese and receiving heavier medical treatments involving long-term oxygen therapy and/or non-invasive ventilation, while our PR program had an effect on anxiety and depression in patients with COPD. This suggests that PR may improve anxiety and depression on a short-term basis after PR but that this effect is not maintained in the long term. Therefore, our results emphasise a distinctive characteristic of severe asthma in comparison to COPD with a lower impact of PR on anxiety and depression in the long term. However, a poor control of asthma is related to most frequent anxiety/depression, especially in 65-year-old obese women with FEV1 inferior to 60% of the theoretical value [29]. The psychological impact of repeated exacerbations leading to repeated systemic corticosteroids treatments may contribute to recurrent mood disorders long time after PR. These results suggest the need to adapt PR programs in severe asthma by incorporating a longer and more regular psychological follow-up that includes emotion management, for instance through cognitive behavioural therapy approach, self-hypnosis or relaxation.

Our study has limitations. It is a retrospective observational study. The study sample is small however severe asthma is akin to “rare diseases” [30]. Patients were not randomised and the choice to join the home-based PR program was based on the patient's personal preference and/or on the absence of a local PR centre. The strength of our study relies on the fact that it reports original results on a short PR program (8 sessions vs 20 to 30 sessions in outpatient programs) entirely performed at home, including educational and final assessments, conducted by a trained interdisciplinary team specialised in PR, integrating immediately changes in favourable health behaviours in the patient's daily life, with the regular presence of his/her relatives and explaining, at

Table 2
Exercise tolerance, anxiety, depression and quality of life at baseline, post-pulmonary rehabilitation (PR) and at 12-month follow-up (M12) in patients with severe asthma and chronic obstructive pulmonary disease (COPD).

	Baseline	Post-PR	ES post-PR	M12	ES M12	Global p
6MST, number of steps						
Severe asthma	450 ± 148	504 ± 150 p = 0.043	+0.35	538 ± 163 p = 0.016	+0.54	0.003
COPD	407 ± 142	466 ± 151 p < 0.001	+0.41	460 ± 181 p = 0.004	+0.33	< 0.001
VSRQ, score						
Severe asthma	32.2 ± 12.4	38.7 ± 15.8 p = 0.119	+0.45	39.0 ± 18.6 p = 0.049	+0.42	0.039
COPD	32.7 ± 15.4	40.4 ± 16.4 p < 0.001	+0.49	38.8 ± 16.9 p < 0.001	+0.37	< 0.001
HAD, score						
Severe asthma	17.9 ± 6.6	14.8 ± 7.5	−0.43	16.7 ± 10.0	−0.14	0.197
COPD	17.8 ± 7.1	14.8 ± 7.7 p < 0.001	−0.41	14.4 ± 7.9 p < 0.001	−0.45	< 0.001
HAD-A, score						
Severe asthma	9.8 ± 3.3	8.4 ± 3.7	−0.41	9.3 ± 4.9	−0.12	0.292
COPD	10.1 ± 4.7	8.7 ± 4.5 p < 0.001	−0.31	8.5 ± 4.7 p < 0.001	−0.34	< 0.001
HAD-D, score						
Severe asthma	8.0 ± 4.0	6.4 ± 4.4	−0.38	7.4 ± 5.9	−0.13	0.235
COPD	7.7 ± 4.0	6.1 ± 4.1 p < 0.001	−0.41	5.9 ± 4.5 p < 0.001	−0.43	< 0.001

ES: effect size, HAD: Hospital Anxiety Depression scale (-A: anxiety, -D: depression), VSRQ: Visual Simplified Respiratory Questionnaire, 6MST: 6-Minute Stepper test.

Table 3
Comparison of the evolution of the exercise tolerance, anxiety, depression and quality of life post-pulmonary rehabilitation vs at baseline between patients with severe asthma and chronic obstructive pulmonary disease (COPD).

	Severe asthma	COPD	p	Effect size
6MST, number of steps				
post-PR - baseline	+86.8 ± 85.8	+56.1 ± 98.0	0.210	−0.32
M12 - baseline	+70.2 ± 104.9	+52.2 ± 131.0	0.436	−0.14
VSRQ, score				
post-PR - baseline	+8.8 ± 13.8	+6.9 ± 12.6	0.277	−0.15
M12 - baseline	+6.8 ± 11.9	+6.1 ± 16.2	0.841	−0.05
HAD-A, score				
post-PR - baseline	−1.7 ± 2.9	−1.4 ± 3.5	0.702	0.08
M12 - baseline	−0.5 ± 4.8	−1.6 ± 3.9	0.311	−0.27
HAD-D, score				
post-PR - baseline	−1.5 ± 2.9	−1.4 ± 3.5	0.911	0.02
M12 - baseline	−0.7 ± 5.1	−1.8 ± 4.1	0.260	−0.26

least partially, the sustainability of the results at 1 year.

In conclusion, home-based PR is associated with an improvement in exercise tolerance and in the quality of life of patients with severe asthma on a long-term basis. Although these results have to be confirmed by multicenter and prospective studies, they point out the interest of PR in severe asthma, which is likely to ease the burden of the disease for the patient, his/her relatives and society.

Contributions to the study

JMG, TG, BW substantially contributed to the conception and design of the work.

JMG, JC, SF, OLR, TG, BW, CC substantially contributed to the acquisition, analysis, or interpretation of data.

JMG, JC, BW, CC drafted the manuscript.

JMG, JC, SF, OLR, TG, BW, CC critically revised the manuscript for important intellectual content.

JMG, JC, SF, OLR, TG, BW, CC gave final approval of the version to be published.

Conflicts of interest

The authors have no conflict of interest in relation to the subject of this study to declare.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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