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Effectiveness of Pulmonary Rehabilitation on Severe Asthma Outcomes: A Pre–Post Study

Émilie Margoline[1] | Emeline Cailliau[2] | Sarah Gephine[3,4] | Stéphanie Fry[5,6] | Olivier Le Rouzic[5] | Jean-Marie Grosbois[4] | Cécile Chenivesse[5,6]

[1]Univ. Lille, CHU Lille, Lille, France | [2]Biostatistics Department, CHU Lille, Lille, France | [3]Univ. Lille, Univ. Artois, Univ. Littoral Côte D'opale, ULR 7369-Urepsss, Lille, France | [4]FormAction Santé, Pérenchies, France | [5]CNRS, Inserm, Institut Pasteur de Lille, U1019, UMR 9017, CIIL, Center for Infection and Immunity of Lille, Univ. Lille, CHU Lille, Lille, France | [6]CRISALIS, F-CRIN Inserm Network, Toulouse, France

Correspondence: Cécile Chenivesse (cecile.chenivesse@chu-lille.fr)

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To the Editor,

Severe asthma is the main cause of asthma burden, morbidity and asthma-related healthcare costs. Although biologics transformed the prognosis, they are mainly effective in type-2 phenotypes, where they exhibit a wide range of responses [1], leaving many patients uncontrolled. Pulmonary rehabilitation (PR) is a transdisciplinary programme improving asthma control in non-severe asthma [2, 3]. In this exploratory study, we aimed to evaluate the effect of PR on severe asthma outcomes.

We conducted a single-centre retrospective cohort study. Adults with severe asthma referred for home-based PR between June 2017 and December 2020 were included. Socio-demographic, clinical and functional data were prospectively collected using CareItou software (French data protection authority: 1413001). Participants signed a written consent. The study was approved by the Committee for the Evaluation of Observational Research Protocols of the French Society for Respiratory Diseases (2021-054). The primary objective was to assess changes in asthma control before and after PR using the asthma control test (ACT). Secondary objectives included evaluating changes in the annual number of severe asthma exacerbations (glucocorticoid intake for at least 3 days and/or hospitalisation and/or emergency room admission), the annual cumulative glucocorticoid dose (self-reported combined with medical record review), airway obstruction (FEV_1), hyperventilation symptoms (Nijmegen score) and anxiety and depression symptoms (Hospital Anxiety and Depression Scale [HADs] scores). Study endpoints were evaluated before PR (M0), at the end of PR (M2), and at 6 (M8) and 12 months (M14). The home-based PR programme was previously described [4]. Briefly, it consisted of an 8-week programme with weekly supervised 90-min sessions including educational and self-management strategies and physical training. Between sessions, patients performed physical training and followed a self-management plan on their own. Statistical analysis was performed using SAS software. Changes in outcomes between M2, M8, M14 and M0 were evaluated using a mixed linear model (covariance pattern) which included time as a fixed effect and an unstructured covariance matrix to account for the correlation between repeated measures. Changes and their 95% CI were estimated using linear contrasts. In cases where residuals deviated from normality, differences between M0–M2, M0–M8 and M0–M14 were assessed using the Wilcoxon signed-rank test. For each outcome, missing values were handled using multiple imputation procedures under the missing at random assumption using a regression switching approach (chained equation with

Abbreviations: ACT, asthma control test; FEV1, forced expiratory volume in one second; HADs, hospital anxiety and depression scale; MCID, minimal clinically important difference; PR, pulmonary rehabilitation.

Jean-Marie Grosbois and Cécile Chenivesse contributed equally to the work.

TABLE 1 | Changes in outcomes at M2, M8 and M14 compared to baseline before and after multiple imputation.

Variable	M0	M2	M8	M14	*p*	M2–M0	*p*	M8–M0	*p*	M14–M0	*p*
Before multiple imputation											
ACT (score)	11.0 [8.0 to 16.0] (*n* = 49)	13.5 [10.0 to 18.5] (*n* = 40)	14.0 [10.0 to 18.0] (*n* = 34)	15.0 [9.5 to 19.0] (*n* = 32)	—	1.0 [0.0 to 4.0] (*n* = 39)	<0.01	2.0 [1.0 to 5.0] (*n* = 33)	<0.01	1.0 [0 to 6.0] (*n* = 31)	0.01
FEV_1 (L)	1.4 [0.9 to 2.8] (*n* = 48)	—	1.4 [0.9 to 2.3] (*n* = 30)	1.1 [0.8 to 2.7] (*n* = 26)	—	—	—	0.1 [−0.2 to 0.2] (*n* = 30)	0.64	−0.0 [−0.2 to 0.1] (*n* = 25)	0.65
Nijmegen (score)	25.1 ± 11.0 (*n* = 46)	19.5 ± 12.7 (*n* = 40)	19.9 ± 12.1 (*n* = 28)	18.8 ± 12.1 (*n* = 23)	<0.01	−4.8 [−7.3 to 2.4] (*n* = 40)	<0.01	−5.8 [−8.0 to −2.5] (*n* = 26)	<0.01	−4.9 [−9.0 to −0.7] (*n* = 19)	0.02
HAD-A (score)	10.2 ± 4.6 (*n* = 50)	7.9 ± 4.5 (*n* = 47)	8.2 ± 4.7 (*n* = 38)	8.5 ± 6.0 (*n* = 29)	<0.01	−2.3 [−3.6 to −1.0] (*n* = 47)	<0.01	−1.9 [−3.2 to −0.6] (*n* = 38)	<0.01	−1.5 [−2.8 to −0.2] (*n* = 29)	0.02
HAD-D (score)	7.6 ± 4.1 (*n* = 50)	5.5 ± 4.1 (*n* = 47)	6.0 ± 4.8 (*n* = 38)	5.0 ± 4.7 (*n* = 30)	<0.01	−2.2 [−3.1 to −1.3] (*n* = 47)	<0.01	−1.6 [−2.6 to −0.5] (*n* = 38)	<0.01	−2.1 [−3.7 to −0.5] (*n* = 30)	<0.01
After multiple imputation											
ACT (score)	11.0 [8.0 to 16.0]	13.4 [10.2 to 17.9]	14.1 [9.4 to 18.7]	13.6 [9.2 to 18.8]	—	1.3 [0.2 to 4.0]	<0.01	2.0 [−1.0 to 5.1]	<0.01	1.2 [−0.7 to 5.1]	<0.01
FEV_1 (L)	1.4 [0.9 to 2.8]	—	1.6 [0.9 to 2.7]	1.3 [0.9 to 2.8]	—	—	—	0.1 [−0.3 to 0.3]	0.57	−0.0 [−0.3 to 0.2]	0.41
Nijmegen (score)	25.0 ± 11.2	19.5 ± 14.0	19.9 ± 16.0	18.8 ± 17.6	<0.01	−5.9 [−8.6 to −3.2]	<0.01	−3.6 [−8.1 to 0.8]	0.11	−5.2 [−10.2 to −0.2]	0.04
HAD-A (score)	10.2 ± 4.6	7.9 ± 4.6	8.2 ± 5.3	8.5 ± 7.8	<0.01	−2.4 [−3.6 to −1.2]	<0.01	−2.2 [−3.7 to −0.6]	<0.01	−1.6 [−3.3 to 0.1]	0.06
HAD-D (score)	7.6 ± 4.1	5.5 ± 4.1	6.0 ± 5.4	5.0 ± 6.0	<0.01	−2.2 [−3.1 to −1.3]	<0.01	−1.7 [−2.8 to −0.6]	<0.01	−1.9 [−3.5 to 0.3]	0.02

Note: Values at M0, M2, M8 and M14 are expressed as mean ± standard deviation or median and interquartile range [Q1–Q3]. Differences between values (M2–M0, M8–M0 and M14–M0) are expressed as mean [95% confidence interval] from linear mixed-effect model or median [Q1–Q3].

Abbbreviations: ACT, asthma control test; FEV1, forced expiratory volume in 1 s; HAD, hospital anxiety depression scale; PR, pulmonary rehabilitation.

Summary

- In severe asthma, pulmonary rehabilitation is associated with improved asthma control.
- It could also be associated with reduced rate of severe exacerbations and use of glucocorticoids.

20 imputations), with the predictive mean matching method for continuous variables and logistic regression for qualitative variables. Estimates from mixed linear models obtained in the imputed datasets were combined using the Rubin's rules. Wilcoxon signed-rank test statistics were pooled over the imputed datasets by calculating the D_2-statistic (after standardisation and squaring) and statistical significance was assessed according to the methodology proposed by Li [5]. The significance level was 5%.

Of the 50 individuals included, 3 did not complete PR (amputation [1], iterative hospitalisations [1] and patient's request [1]). Of the remaining 47 individuals, 38 were assessed at M8 and 30 at M14. Patients were mainly women ($n = 39$, 78.0%), with a median age of 59.0 years [IQR: 46.0–65.0] and most were non-smokers ($n = 28$, 56.0%). All patients received high doses of inhaled corticosteroids combined with long-acting-beta2-agonists, 32 (64.0%) long-acting-muscarinic-antagonists, 17 (34.7%) daily glucocorticoids and 21 (43.8%) a biologic, introduced more than 6 months before PR in 14 (66.7%) patients.

Median ACT score was higher at short- and long-terms following PR compared to baseline (Table 1). Among patients with available data, 14 ($n = 39$, 35.9% [IQR: 20.8–50.9]) exceeded the minimal clinically important difference (MCID) of three points [6] at M2, 15 ($n = 33$, 45.5% [IQR: 28.4–62.4]) at M8 and 12 ($n = 31$, 38.7% [IQR: 21.6–55.9]) at M14.

The annual rate of severe exacerbations decreased significantly from 3.0 [IQR: 1.0–6.0] to 1.5 [IQR: 0.0–4.5] in the year after PR ($p < 0.01$) ($n = 33$), representing a median reduction of 50.0% [IQR: −10.0 to 100.0] ($n = 29$). Cumulative glucocorticoid use also decreased from 2240.0 mg [IQR: 250.0–5040.0] to 1200.0 mg [IQR: 0.0–4290.0] ($p < 0.01$) ($n = 33$), a median reduction of 53.0% [IQR: 3.5–100.0] ($n = 29$). After multiple imputation, the annual rate of severe exacerbations decreased from 3.0 [IQR: 1.0–5.9] to 1.1 [IQR: 0.0–4.1] ($p < 0.01$) and the cumulative glucocorticoid use from 2331.0 mg [IQR: 252.0–4611.0] to 1105.0 mg [IQR: 0.0–3679.0] ($p < 0.01$). Among the 23 patients receiving more than 1 g of glucocorticoids the year before PR, 4 (17.4%) were weaned and 6 (26.1%) had their cumulative dose halved the year after PR.

We observed no change in FEV1. Hyperventilation, anxiety and depressive symptoms were all but the M8 Nijmegen score reduced after PR (Table 1).

In this exploratory study, we observed both short- and long-term improvements in asthma control following PR, as assessed by the ACT score, which is highly relevant in clinical practice [7] and well correlated with the Asthma Control Questionnaire used in randomised controlled trials [8]. Previous studies reported a greater effect [2, 3] in asthmatics of any severity, who were not systematically assessed in an asthma centre, an intervention known to address many factors contributing to lack of control [3, 9]. We also noted a 50% reduction in severe exacerbation rate and glucocorticoid use, aligning with biologic's clinical response definition, although caution is needed due to missing data.

This study is limited by its retrospective, monocentric and uncontrolled design; however, it reports original data providing an estimation of the effect of PR on severe asthma outcomes, with the aim of guiding future controlled studies. The population size, although relatively large for an uncommon disease, did not permit subgroup analysis.

In conclusion, our findings suggest that PR may have a role in managing patients who are ineligible for and/or uncontrolled by biologics beyond the management of respiratory disability.

Author Contributions

E.M. conceived and designed the analysis, collected the data, performed the analysis, and wrote the paper. E.C. conceived and designed the analysis, performed the analysis, and wrote the paper. S.G. conceived and designed the analysis, collected the data, and wrote the paper. S.F. conceived and designed the analysis, and collected the data. O.L.R. conceived and designed the analysis, and collected the data. J.M.G. conceived and designed the analysis, collected the data and wrote the paper. C.C. conceived and designed the analysis, collected the data, performed the analysis and wrote the paper.

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Conflicts of Interest

Émilie Margoline declares no conflicts of interest. Emeline Cailliau declares no conflicts of interest. Sarah Gephine declares no conflicts of interest. Stéphanie Fry declares personal fees from AstraZeneca, GSK and Sanofi and congress support from Sanofi. Olivier Le Rouzic reports personal fees and non-financial support unrelated to the submitted work from AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, GlaxoSmithKline, MSD France, Vertex and Vitalaire. Olivier Le Rouzic is principal investigator in studies for Vertex and CSL Behring. Jean-Marie Grosbois declares personal fees from AstraZeneca, Boehringer-Ingelheim, Chiesi, CSL Behring and GSK and congress support from Boehringer Ingelheim and GSK. Cécile Chenivesse declares research grants from AstraZeneca, GSK, Santelys and Novartis, personal fees from ALK-Abello, AstraZeneca, Boehringer-Ingelheim, Chiesi, Sanofi and GSK and congress support from AstraZeneca, Boehringer Ingelheim, Chiesi, and Novartis, outside the submitted work.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Émilie Margoline
Emeline Cailliau
Sarah Gephine
Stéphanie Fry
Olivier Le Rouzic
Jean-Marie Grosbois
Cécile Chenivesse

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