Less exacerbations and sustained asthma control 12 months after high altitude climate treatment for severe asthma

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SUPPORTING INFORMATION

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Less exacerbations and sustained asthma control 12 months after high altitude climate treatment for severe asthma

To the Editor,

Despite comprehensive asthma treatment guidelines and the availability of effective medication and promising new biologicals, management of patients with severe asthma is still challenging. Severe uncontrolled asthma is a burden for patients and caregivers representing a major cause of disability, poor quality of life, and high health resource utilization. Current international treatment guidelines include referral for assessment in specialized asthma centers, evaluation of the eligibility for biologicals, and non-pharmacological add-on interventions, such as allergen avoidance measures and high altitude climate treatment (HACT).[1,2] HACT results in improvement of all aspects of asthma control especially in adult patients with severe asthma.[3] HACT combines a 12-week multidisciplinary treatment program with environmental trigger avoidance in the alpine climate and is provided throughout the year. It is unclear how long these treatment effects are sustained, although it is known that some patients have a long-time advantage of HACT. Therefore, we evaluated the long-term effectiveness of HACT on exacerbations and asthma control in patients with severe asthma.

A prospective observational cohort study with a 12-month follow-up period at sea level was carried out between 2008 and 2011.[4] Four follow-up study assessments consisting of questionnaires were planned for each patient at 0, 3, 6, and 12 months after HACT. All patients provided written informed consent. The study was approved by the institutional review board of the Academic Medical Centre of the University of Amsterdam and is registered at the Netherlands Trial Register NTR1277. Patients included in the study were adults with uncontrolled asthma despite using high doses of inhaled corticosteroids combined with long-acting bronchodilators for more than 1 year, who experienced at least two severe exacerbations requiring a course of oral corticosteroids during the past year, or received maintenance oral corticosteroid therapy. The primary outcome of this study was the change in exacerbation rate during the year after compared to the year before admission to the Dutch Asthma Centre Davos, Switzerland (altitude 1560 m). An exacerbation was defined as the requirement for an oral steroid burst, based on pharmacy data. Asthma-related hospitalization was self-reported by the patient.

TABLE 1 Exacerbations, hospitalizations, and oral corticosteroid use before and after high altitude treatment

	Year before treatment	Year after treatment	% decrease	*P*-value
Number of exacerbations per patient (pharmacy data)	3 (4) n = 97	2 (3) n = 95	34	0.000
Number of exacerbations per patient (patient reported)	5 (6)	2 (4) n = 98	60	0.000
Number of hospitalized patients	51 (50.5%)	28 (32%) n = 87	36	0.014
Number of hospitalizations per patient	2 (2)	0.5 (2.2)	75	0.010
Need for maintenance oral corticosteroids (pharmacy data)	31 (33%) n = 93	33 (34%) n = 97	0	1.0
Required dose (mg) of maintenance oral corticosteroids (pharmacy data)	10 (10)	10 (10)	0	0.684

Data are presented as n (%) or median (interquartile range).

Secondary outcomes included use and dose of oral corticosteroids during follow-up, asthma control (ACQ), and asthma-related quality of life (AQLQ).

Hundred and eighty patients were asked to participate in the study, and 101 patients (58%) completed the 12-month follow-up period (Figure S1). The majority of patients were female, middle-aged, had multimorbidities and required chronic oral steroid treatment (Table S1). Differences between those lost to follow up and completers are shown in Table S2. Those lost to follow up were significantly younger and had significantly higher ACQ scores at discharge. A significant decrease in exacerbations (34% decrease) and hospitalizations (36% decrease) was observed compared to the year before HACT (Table 1). There was no change in the need or amount of maintenance oral corticosteroid use at 12 months before compared to 12 months after HACT (Table 1). There was a decrease in ACQ from admission to 12 months after discharge, the ACQ score at admission was median (IQR) 3.0 (1.37), at discharge 1.0 (1.5), at follow-up by 3 months 2.0 (2.0), at 6 months 2.0 (2.0), at 12 months 2.3 (2.0) (Figure 1A). There was an increase in AQLQ score from admission with a median (IQR) 4.0 (1.22), to discharge 6.0 (1.1), at follow-up by 3 months 5.2 (1.6), at 6 months 5.1 (1.4), at 12 months 5.0 (1.6) (Figure 1B). After twelve-month follow-up, there were statistically significant and clinically relevant sustained improvements in ACQ and AQLQ compared to baseline ($P < 0.000$).

Our study is the first to show a decrease in exacerbations and sustained improvement in asthma control up to 12 months after HACT in adult patients with uncontrolled severe asthma. However, the observational study design makes it difficult to identify the driving mechanism for the observed improvement. A characteristic feature of HACT in the alpine climate of Davos is the absence of most triggers. Triggers are known to stimulate and maintain airway inflammation, and trigger avoidance (house dust mite, pollen, air pollution) is recommended in treatment guidelines.[5] We hypothesize that trigger avoidance through climate change to high altitude can change the ongoing airway inflammation.[4,6,7] In addition, the extensive multidisciplinary treatment program including education in trigger avoidance at home and optimization of adherence to therapy will help to sustain the effect. The 12-week multidisciplinary treatment program included a personalized exercise program with various indoor and outdoor activities, optimization of

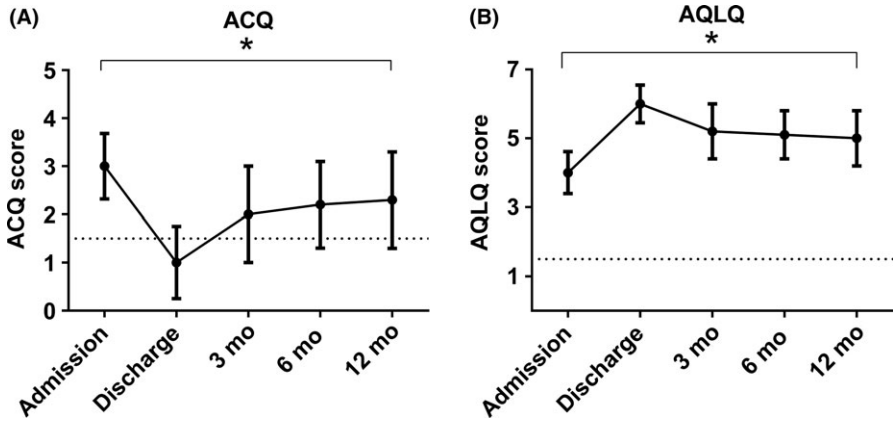

FIGURE 1 Asthma control and asthma-related quality of life up to 12 mo after high altitude climate treatment. A, Asthma Control Questionnaire (ACQ) scores at admission, discharge, 3-, 6-, and 12-month follow-up in 101 patients with severe asthma. Data are presented as median (interquartile range). The dashed line indicates an ACQ score of 1.5. There is a clinically relevant difference of 0.7 between admission and 12-mo follow-up. B, Asthma-related Quality of Life Questionnaire (AQLQ) scores at admission, discharge, 3-, 6-, and 12-month follow-up in 101 patients with severe asthma. Data are presented as median (interquartile range). There is a clinically relevant difference of 1.0 between admission and 12-mo follow-up

medication inhalation techniques, interactive patient education sessions, psychosocial therapy sessions addressing disease management skills, behavioral aspects of living with a chronic disease and problems such as anxiety, stress, and depression and optional respiratory physiotherapy and dietary counselling. All patients were provided with a personalized asthma action plan and instructed how to step up treatment and when to consult their pulmonologist. The provided treatment program fits with the recently proposed treatable traits for chronic airway disease and likely contributed to the sustained asthma control during 12-month follow-up.[8] A subgroup of patients with a need for maintenance oral steroids might benefit from phenotype specific monoclonal antibody therapy in the near future.

There are some inherent limitations to an observational study, such as the lack of a control group with a similar program at sea level. Our findings from a single center may have limited generalizability to other HACT centers. Furthermore, our study does not provide insight to the possible mechanisms for the observed effect during follow-up, and biomarker data are lacking. The significant differences on age and asthma control at discharge between the patients who did and did not start follow-up lead to bias in our data. Therefore, our results should be interpreted with caution. The beneficial effect of a 12-week HACT in adults with severe asthma can be predicted by different patient characteristics, such as age, blood eosinophils, and degree of asthma control before admission.[9] Further patient characterization can help us to identify the patients with long-term advantage or more rapid deterioration after HACT.

In conclusion, this study shows that HACT results in less exacerbations and sustained long-term asthma control in patients with uncontrolled severe asthma. HACT could be an adequate treatment option for uncontrolled severe asthmatic patients besides all other new treatment options, especially biologicals. Future trials and cost-effectiveness studies are needed to determine the best position for HACT among all other treatment options.

CONFLICTS OF INTEREST

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: LR declares working as a pulmonologist and researcher at the Dutch Asthma Center Davos. KF declares working as a researcher at the Dutch Asthma Center Davos. SH and EW have no conflict of interest to report. EB reports research grants for the department and personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Roche, Sanofi Regeneron, Teva, Vectura, outside the submitted work.

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alpine, altitude, asthma, climate, severe

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