

Anti-interleukin-5/anti-interleukin-5 receptor α treatment improves self-reported work productivity in patients with severe eosinophilic asthma: a prospective cohort trial

Lina Brinkmann^{1,3}, Jan Fuge ^(1,2,3), Tobias Welte ^(1,2,4), Hendrik Suhling^{1,2,4} and Nora Drick ^(1,2,4)

¹Department of Respiratory Medicine and Infectious Diseases, Hannover Medical School, Hannover, Germany. ²Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), member of the German Center for Lung Research (DZL), Hannover, Germany. ³These authors contributed equally.

Corresponding author: Nora Drick (drick.nora@mh-hannover.de)

Check for updates	Shareable abstract (@ERSpublications) Treatment with IL-5/anti-IL-5R α antibodies leads to a significant increase in self-reported work productivity and patients are substantially less negatively affected by their disease https://bit.ly/ 4bb3qaW Cite this article as: Brinkmann L, Fuge J, Welte T, <i>et al.</i> Anti-interleukin-5/anti-interleukin-5 receptor α treatment improves self-reported work productivity in patients with severe eosinophilic asthma: a prospective cohort trial. <i>ERJ Open Res</i> 2024; 10: 00374-2024 [DOI: 10.1183/23120541.00374-2024].
Copyright ©The authors 2024 This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org Received: 12 April 2024 Accepted: 12 June 2024	Abstract Background Severe asthma affects the working life of millions of people worldwide. Interleukin (IL)-5/ anti-interleukin-5 receptor α (IL-5Rα) antibodies are highly effective in reducing symptoms in patients with severe eosinophilic asthma. We analysed effects of anti-IL-5/anti-IL-5Rα treatment on self-reported productivity and absenteeism at work in patients with severe eosinophilic asthma. <i>Methods</i> In this prospective single-centre study, patients with severe eosinophilic asthma received a questionnaire assessing their actual occupational status and the influence asthma has on their work life, productivity and missed days at work prior to initiation of antibody treatment and after 6 and 12 months of therapy. Among others, the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) was used. <i>Results</i> Out of 54 patients with a median age of 60 years, 27 (50%) were employed. In addition to an increase in asthma control and lung function, self-reported productivity increased significantly with a decrease on the WPAI:SHP from 30% (interquartile range (IQR) 20–50%) to 10% (IQR 0–27.5%) under treatment (p=0.001). Furthermore, self-reported missed days at work were reduced from 2 days·month ⁻¹ (IQR 1.75–6 days·month ⁻¹) to 0 days·month ⁻¹ (IQR 0–2 days·month ⁻¹ ; p=0.067). At baseline 22 employed patients (81%) stated they were affected at work by their asthma. After 12 months of treatment, this number decreased to eight patients (30%; p=0.038). <i>Conclusions</i> This prospective analysis could prove the substantial impact severe asthma has on patients' working life. Anti-IL-5/anti-IL-5Rα treatment in patients with severe eosinophilic asthma leads to a significant increase in self-reported productivity at work, and after 12 months of treatment patients state substantially fewer negative effects on their working situation.
	Introduction Bronchial asthma is a common respiratory disease leading to symptoms such as coughing, wheezing, shortness of breath and chest tightness, and thereby affects millions of people worldwide in their daily life [1]. Approximately 3–10% of asthma patients have severe asthma, representing a heterogenous group of patients in which symptoms are not controlled by inhaled medication [2]. In these patients, frequent exacerbations, distinct symptoms and numerous medication side effects represent a substantial burden, leading to a reduced quality of life (QoL) in private but also influencing occupational life [3]. In addition to missed days at work and a negative impact on work productivity, patients are concerned about the perception of colleagues [3]. In patients with severe asthma, disease control is directly linked to work productivity, given that patients with uncontrolled severe asthma show lower productivity and more

absenteeism from work than patients in whom symptoms are controlled [4, 5]. For patients with severe asthma, several monoclonal antibodies (mepolizumab, reslizumab, benralizumab, dupilumab, omalizumab, tezepelumab) that interfer directly with the interleukin (IL)-5 or IL-5 receptor a (IL-5R α), IL-4/IL-13 receptor, IgE or thymic stromal lymphopoietin have been approved. Treatment with these antibodies is highly effective, leading to improved lung function, reduced exacerbations and reduced oral corticosteroid (OCS) intake [6–11]. *Post hoc* meta-analyses and retrospective data indicate that treatment with IL-5 or IL-5R α antibodies in patients with severe eosinophilic asthma (SEA), a phenotype mainly caused by type 2 inflammation and associated with elevated eosinophilic granulocytes, might not only control symptoms but also lead to improved work productivity [12, 13]. In this study, we prospectively analysed the effect of anti-eosinophilic treatment in patients with SEA on work productivity and missed days at work.

Methods

Setting

In this prospective, single-centre cohort study, 54 patients with SEA treated at the severe asthma outpatient clinic of Hannover Medical School were included between January 2020 and June 2022 and followed up until July 2023. The study was conducted in accordance with the principles of the Declaration of Helsinki. Patients provided written informed consent and analyses were performed with approval of the local institutional review board of Hannover Medical School (No. 8050_BO_K_2018).

Treatment

All patients included in the study were diagnosed with SEA by a specialised pulmonologist based on the European Respiratory Society (ERS)/American Thoracic Society (ATS) definition [14]. All patients were treated with maximised inhaler therapy (medium- or high-dose inhaled glucocorticoids and a long-acting β_2 -agonist, partially with a second or third controller) and fulfilled criteria for initiation of anti-eosinophilic antibody treatment. Patients received either anti-IL-5 therapy with mepolizumab or anti-IL-5R α treatment with benralizumab.

Routine follow-up

Routine follow-up included spirometry or body plethysmography standardised to ERS/ATS guidelines, measurement of exhaled nitric oxide (eNO), capillary blood gas analysis and laboratory testing (differential blood count, IgE) if indicated. Asthma control was assessed by the Asthma Control Test (ACT) and patients were asked about symptoms, comorbidities and exacerbations within the last 6 months and changes in medication at each follow-up visit. Treatment response to antibody therapy was assessed using the Biologic Asthma Response Score (BARS). According to BARS, patients can be categorised as responders, partial responders and non-responders using three main criteria: reduction of exacerbations, reduction of OCS and improvement of asthma control; and one optional criterion: improvement of lung function [15]. Achievement of clinical remission, defined by the absence of systemic corticosteroids for the treatment of asthma, absence of exacerbations, absence of significant symptoms (ACT \geq 20 points) and a stabilised or optimised lung function, was assessed after 12 months [16].

Questionnaire assessment

In addition to the routine follow-up assessment, patients were asked to fill out a questionnaire assessing their actual occupational status and the influence asthma has on their work life (negative or positive) using multiple-choice questions. Furthermore, missed days at work were assessed. Productivity at work was assessed using the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP). Questions two and four result in the subscore for absenteeism (work time missed), question five (the degree to which the problem affected productivity while working) assesses presenteeism and question six (the degree to which the problem affected regular activities) assesses activity impairment. Scores range from 0% to 100%, with higher percentages indicating greater impairment and less productivity. QoL was assessed using the EuroQol EQ-5D-3L-questionnaire including the visual analogue scale ranging from 0 points (worst imaginable health state) to 100 points (best imaginable health state). Patients were asked to fill out the questionnaire prior to start of antibody treatment (baseline) and after 6 months and 12 months of treatment.

Statistical analysis

Continuous variables are stated as median and interquartile range (IQR), categorical variables are shown as n (%). Comparisons between baseline and 12 months were conducted using Wilcoxon test, paired t-test or McNemar's test, as appropriate. Logistic regression analysis was used to determine the impact of employment on clinical remission. Violin plots and Sankey charts are used to show data over time. A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics and asthma control

In total, 54 patients with SEA were included in the study. Median patient age was 60 years (IQR 53–69 years), 59% of patients were female and the most frequent comorbidities were COPD disease (46%), chronic rhinosinusitis with nasal polyps (17%) and chronic rhinosinusitis without nasal polyps (13%). At baseline, 31 patients (57%) received mepolizumab and 23 patients (43%) were treated with benralizumab. According to the BARS, 30 patients (56%) could be classified as responders, 18 (33%) as partial responders and six (11%) as non-responders. The ACT score increased from a median of 14 points (IQR 11–16 points) prior to antibody treatment to 18 points (IQR 14–22 points) after 12 months of therapy (p=0.001). At the same timepoint, forced expiratory volume in 1 s improved from 62% predicted (IQR 48–75%) to 71% predicted (IQR 52–83%) (p=0.001) and the median number of exacerbations within the past 12 months decreased from two (IQR 1–3) to one (IQR 1–2) (p=0.655). Changes in lung function, ACT score and blood eosinophils from baseline to follow-up are depicted in figure 1. The number of patients being hospitalised due to their bronchial asthma decreased from 16 (30%) to 1 (2%) after 12 months (p<0.001). At baseline six patients (11%) stated hospitalisation due to other reasons than asthma within the last 6 months; at 12 months this number decreased to three (6%) (p<0.001). The number of patients on OCS decreased from 29 (54%) at baseline to 14 (26%) after 12 months and the median OCS

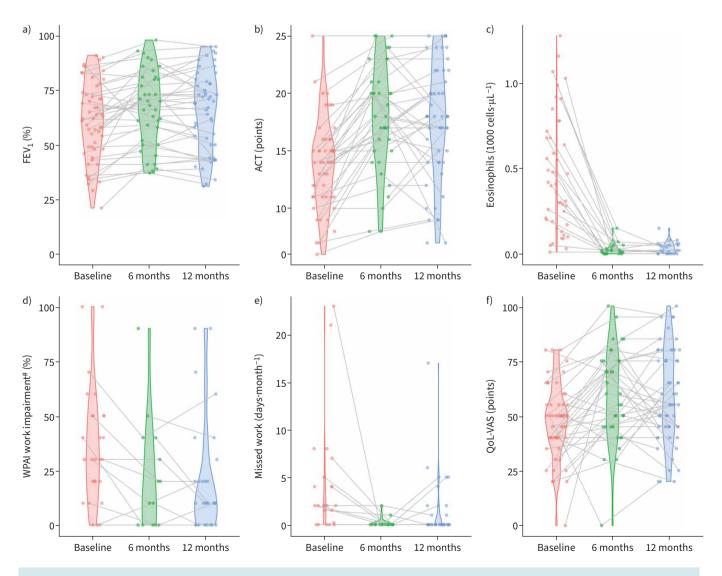


FIGURE 1 Change from baseline to 6 months and 12 months in a) lung function (forced expiratory volume in 1 s (FEV₁)), b) Asthma Control Test (ACT), c) blood eosinophil count, d) Work Productivity and Activity Impairment (WPAI): specific health problem questionnaire, e) missed days at work and f) quality of life visual analogue scale (QoL-VAS). a-c, f show data from all patients (n=54), d, e show data for employed patients (n=27). [#]: data presented as mean±sp because of the distribution of the data.

TABLE 1 Demographics	
Characteristic	Value
Participants (n)	54
Employed/working	27 (50)
Age (years)	60 (53–69)
Sex (female)	32 (59)
Body mass index (kg·m ⁻²)	28.8 (24.5–33.1)
Smoking status	
Never	25 (46)
Former	29 (54)
Pack-years	22 (8–30)
Comorbidities	
Chronic rhinosinusitis without nasal polyps	7 (13)
Chronic rhinosinusitis with nasal polyps	9 (17)
Atopic dermatitis	1 (2)
NSAID hypersensitivity	5 (9)
Medication at baseline	
ICS/LABA (medium or high-dose)	54 (100)
LAMA	47 (87)
LTRA	13 (24)
OCS	29 (54)
OCS dose (mg)	7.5 (5–10)
Mepolizumab	31 (57)
Benralizumab	23 (43)
BARS after 12 months	
Responder	30 (56)
Partial responder	18 (33)
Non-responder	6 (11)
Remission (after 12 months)	29 (54)

Data are presented as median (IQR) or n (%), unless otherwise stated. NSAID: nonsteroidal anti-inflammatory drug; ICS: inhaled corticosteroids; LABA: long-acting β_2 -agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; BARS: Biologics Asthma Response score.

dose could be reduced from 7.5 mg (IQR 5–10 mg) to 5 mg (IQR 4.5–7.6 mg) (p=0.012). After 12 months of treatment, 29 patients (54%) were in clinical remission. Patient characteristics are presented in table 1; information concerning lung function, blood gas analysis, OCS use, exacerbations and hospitalisations is presented in table 2.

Employment situation

At baseline, 27 patients (50%) were employed (full-time or part-time) and 27 (50%) were not employed. Reasons for being not employed were: old age/retirement (n=14, 26%), staying home as a homemaker (n=6, 11%), unemployment (n=3, 6%), occupational disability (n=2, 4%) and being a student (n=2, 4%). Within the 12 months following treatment initiation, the status of the 27 employed patients remained stable in 22 patients and changed in five patients, of whom four patients retired and one patient lost employment due to unknown reasons. Of the six patients classified as homemakers, two started working again and one patient retired. Of the two students, one started working. One unemployed patient became unable to work due to disability. Data concerning the employment status at baseline and changes over time are presented in table 3 and figure 2. Self-reported work productivity assessed by the WPAI:SHP was 30% (IQR 20-50%) at baseline and 10% (IQR 0-2.75%) after 12 months of treatment (p=0.001). Self-reported productivity outside work also increased with a decrease in the WPAI:SHP, from 60% (IQR 40-80%) at baseline to 35% (IQR 12.5-60%) after 12 months of treatment (p=0.001). Changes in the WPAI:SHP and missed days at work from baseline to 6 and 12 months are depicted in figure 1. Employed patients stated an average of missed days at work of 2 days month⁻¹ (IQR 1.75–6 days month⁻¹) at baseline and 0 days month⁻¹ (IQR 0-2 days month⁻¹) after 12 months of biological treatment (p=0.067). Questioning only employed patients, 22 out of 27 patients (81%) stated that asthma has an influence on their working situation at baseline; after 12 months of antibody treatment, this number decreased to eight out of 27 (30%) (p=0.038). At 12 months, two patients (4%) stated troubles with colleagues due to their disease, compared to six patients (12%) at baseline. Results of the work questionnaire are presented in table 3. Of the working patients, 21 (78%) were in clinical remission after 12 months of treatment compared to three patients (30%) of the not-working

	Baseline	6 months	12 months	p-value
Lung function				
FEV ₁ (%)	62 (48–75)	69 (52–81)	71 (52–83)	0.001
FEV ₁ (mL)	1715 (1145–2367)	1870 (1430–2457)	1880 (1410–2545)	0.005
FVC (%)	80 (66–90)	87 (76–94)	83 (74–94)	0.001
FVC (mL)	2640 (1998–3278)	2820 (2268–3518)	2750 (2263–3683)	0.004
MEF _{25-75%} (%)	33 (22–47)	41 (24.75–54.25)	40.5 (24.5–57.5)	0.032
MEF _{25-75%} (mL)	1.05 (0.69-1.62)	1.185 (0.81–1.94)	1.32 (0.78-1.86)	0.072
RV (%)	136.5 (116.25–160.25)	135.5 (110.75–158)	129.5 (111.5–158.25)	0.024
RV (mL)	2745 (2268–3215)	2835 (2215–3712)	2615 (2303–3435)	0.043
eNo (ppb)	30.6 (20-50.5)	27 (12.2–42.2)	25.2 (13.9-45.7)	0.100
Po, (mmHg)	71.9 (66.2–78)	77.8 (65.6–81.9)	75.7 (68.2–82.7)	0.408
P _{co} (mmHg)	38.4 (35.4-40.8)	39 (36-41.6)	39.2 (36.1-41.8)	0.917
Blood eosinophils (cells·µL ⁻¹)	405 (185–690)	20 (0–350)	20 (0–550)	0.001
ocs	29 (54)	15 (39)	14 (26)	0.070
OCS dose (mg·day ^{−1})	7.5 (5–10)	5 (2.5–7.5)	5 (4.5–7.6)	0.003
ACT points	14 (11–16)	18 (15–21)	18 (14–22)	0.001
EQ-5D-3L VAS	50 (40–60)	60 (50-80)	60 (50–80)	<0.001
Patients with hospitalisations due to asthma within the last 6 months	16 (30)	4 (7)	1 (2)	<0.001
Number of hospitalisations	2 (1–2)	1 (1-1)	1	-
Patients with hospitalisations due to reasons other than asthma within the last 6 months	6 (11)	2 (4)	3 (6)	<0.001
Number of hospitalisations	1 (1-2)	1 (1-1)	2 (1–2)	0.317
Patients with exacerbations	32 (59)	12 (22)	14 (26)	0.001
Number of exacerbations	2 (1–3)	1 (1-3)	1 (1-2)	0.655

Data are presented as median (IQR) or n (%). FEV_1 : forced expiratory volume in 1 s; FVC: forced vital capacity;
MEF _{25-75%} : mean expiratory flow at 25–75% of FVC; RV: residual volume; eNO: exhaled nitric oxide; P _O ,: partial
pressure of oxygen; P _{CO} : partial pressure of carbon dioxide; OCS: oral corticosteroids; ACT: Asthma Control
Test; VAS: visual analogue scale.

group (old-age pensioners were not incuded). Logistic regression analysis showed an 8-fold chance to being in remission after 1 year when employed compared to not employed.

Discussion

In this prospective study, the effect of anti-IL-5/anti-IL-5R α treatment on work productivity, missed days at work and overall satisfaction with the employment situation was analysed. By using questionnaires including the WPAI:SHP, we could show that antibody treatment leads to a significant increase in self-reported productivity at work and outside work and a reduction in missed days at work. After 12 months of biological treatment, patients stated substantially fewer negative effects of their asthma disease on their occupational situation.

Asthma, and especially severe or uncontrolled asthma, has a substantial impact on patients' work life. In an international online survey with more than 2000 participants assessing the impact of asthma on their occupational life, nearly three quarters of patients stated that asthma has an impact on their work productivity [3]. Respiratory symptoms due to poor asthma control was the main driver for reduced productivity, alongside absenteeism. In our study numbers are even higher, with 81% of all working patients stating that asthma has an influence on their occupational life, providing evidence for the impact of this disease and stressing the need for disease control. Comparing patients with mild-to-moderate asthma with patients with severe asthma, CHEN *et al.* [17] showed that patients with less controlled symptoms have a higher level of impairment at work. Positive treatment effects of anti-IL-5/anti-IL-5R α antibodies on symptom control in patients with severe asthma is beyond debate and has been proven in

	Baseline	6 months	12 months	p-value
Patients (n)	27	26	25	
Working patients	27 (50)	26 (48)	25 (46)	0.625
WPAI work impairment (presenteeism)	30 (20–50)	15 (0-40)	10 (0–27.5)	0.001
WPAI activity impairment	60 (40-80)	30 (20–70)	35 (12.5–60)	0.001
WPAI work time missed (absenteeism) [#]	9.4±23.4	5.9±15.8	8.5±22.8	0.833
Missed days at work within the last 6 months (days·month ⁻¹)	2 (1.75–6)	0 (0–0.5)	0 (0–1)	0.114
Patients with ≥1 missed days of work within the last 6 months	18 (67)	4 (15)	9 (36)	0.125
Patients affected by asthma at work	22 (67)	2 (11)	8 (24)	0.038
Reduction of working hours	2 (4)	0	1 (2)	
Retraining/change of job	0	1 (2)	2 (4)	
Trouble with colleagues	6 (12)	0	2 (4)	
Termination of employment	3 (6)	0	0	
Satisfaction with work situation				
Really satisfied or satisfied	32 (65)	26 (84)	35 (74)	
Unsatisfied or really unsatisfied	17 (35)	5 (16)	12 (26)	
Number of not-employed patients	27 (50)		29 (54)	
Old-age pension	14 (26)		19 (35)	
Student	2 (4)		1 (2)	
Unemployed	3 (6)		3 (6)	
Homemaker	6 (11)		3 (6)	
Disability pension	2 (4)		3 (6)	

Data are presented as median (interquartile range) or n (%), unless otherwise indicated. [#]: data shown as mean \pm sp because of the distribution of the data.

many trials. ALBERS et al. [12] carried out a post hoc analysis of data from two licensing trials, MENSA and MUSCA, and showed that, in employed patients with SEA, treatment with mepolizumab leads to an overall improvement in work productivity. These results were confirmed in a registry-based study, showing that overall work impairment significantly decreased after initiation of anti-IL-5/anti-IL-5R α therapy [18]. To assess work productivity, the WPAI is broadly used in clinical practice and has been proven to correlate with self-reported asthma outcomes [17]. Nevertheless, the WPAI has not yet been validated specifically for the use in patients with SEA, but studies in other chronic conditions suggest that changes in the WPAI of \geq 20% can be considered clinically relevant [19]. Using the WPAI in a retrospective analysis, we have previously shown that treatment with IL-5/IL-5R α antibodies leads to an improvement in work productivity and a reduction in missed days at work [13]. We can now confirm these results prospectively by showing that 12 months of anti-IL-5/anti-IL-5R α therapy leads to a significant increase in self-reported work productivity and a reduction in absenteeism. This effect seems to be present after only 6 months of antibody treatment, but owing to the worldwide COVID-19 pandemic, many patients did not attend follow-up visits, leading to missing data at the first follow-up timepoint and thereby reducing the significance of the data assessed after 6 months. Our results further highlight how disease control with anti-IL-5/anti-IL-5Rα therapy can influence the emotional affect severe asthma has on a patient's occupational life. Antibody treatment reduced the number of patients stating that asthma has a negative influence on their working situation from 81% to 30% after 12 months; among other things, patients described less trouble with colleagues. Psychological comorbidities (depression and anxiety) are common in asthma patients in private and occupational life [20]. A study with 300 asthma patients showed that one third of patients had psychological distress, correlating significantly with reduced asthma control and being associated with a higher loss in productivity [21]. A large study from Finland with data from 2332 asthmatic and 66 354 non-asthmatic employees showed that the risk of long-term work disability in asthma patients is further increased in patients with depression as a comorbidity [22]. A 2-year prospective cohort study comparing patients with severe and non-severe asthma reported symptoms of anxiety in 38% and symptoms of depression in 25% of patients with severe asthma, compared to 30% and 9% in patients with non-severe asthma [23]. The presence of anxiety and depression also correlates with asthma control [24], highlighting once again the importance of controlling symptoms in patients with severe asthma and keeping comorbidities in mind. From the 54 patients included in our prospective study, 27 (50%) were employed, indicating that half of all patients were not working. In the most affected patients, SEA becomes manifest as late-onset asthma and is therefore often diagnosed in patients who are already retired [25]. In

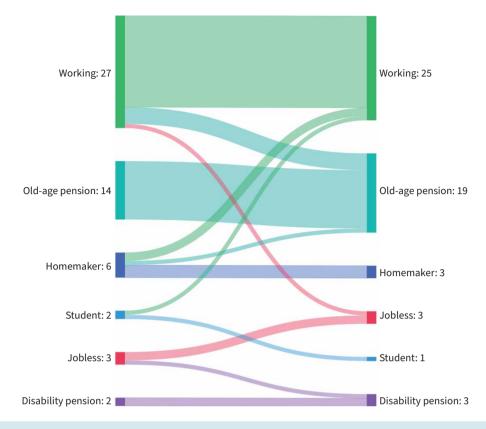


FIGURE 2 Sankey chart of the employment status of all 54 patients at baseline and after 12 months of anti-interleukin (IL)-5/anti-interleukin-5 receptor α (IL-5R α) therapy. The status of the 27 employed patients remained stable in 22 patients and changed in five patients, of whom four patients retired and one patient lost employment due to unknown reasons. Of the six patients at home as homemakers, two started working again and one patient retired. Of the two students, one started working. One unemployed patient became unable to work due to disability.

our cohort, reasons for not working were heterogenous and partly attributable to the patients median age of 60 years, given that patients with asthma have a higher risk of leaving work prior to age 65 years than people without chronic conditions [26], but the results also show that severe asthma leads to work disability and unemployment. A cross-sectional study with more than 2000 working-age adults with asthma showed that severe symptoms of asthma were associated with undesirable employment status, such as unemployment [27]. Because anti-IL-5/anti-IL-5R α therapy is highly effective in reducing asthma symptoms, treatment with these antibodies can help to improve patients' productivity and may also help to keep patients employed, but patients who are already disabled and retired will most likely not return to their jobs. Therefore, it is crucial to prevent patients from becoming unable to work by achieving asthma control as soon as possible. This thesis is supported by data from the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis, which show that in employed patients with axial spondyloarthritis presenteeism predicts upcoming absenteeism, which predicts future work loss. Biological treatment is highly effective in improving overall work impairment, but is less beneficial when it comes to reducing absenteeism, because absenteeism represents a late stage in terms of work impairment that is difficult to reverse [28, 29]. Data assessing the return to work are sparce, but KEAT et al. [30] showed that in patients with ankylosing spondylitis, treatment with infliximab improved the capacity to work and enabled at least some patients to return to work. Rheumatological criteria for clinical remission have long been established for many diseases, and now clinical remission criteria also exist for severe asthma [16]. Considering these criteria, 29 patients (54%) in our study were in remission after 12 months of treatment. Considering working patients, 78% were in remission compared to 30% of the not-working patients, showing an 8-fold chance of being in remission after 1 year when employed. However, this study does not show causality of employment affecting remission and further research is needed to address this question. Besides the affect severe asthma has on a patient's life, it is also associated with substantial societal costs, especially in patients regularly treated with OCSs [31]. A comparison of asthma-related costs between the different grades of severity shows that costs are more than twice as high in patients with severe asthma than in patients with moderate asthma [32]. Exacerbations, and especially hospitalisations, are one of the main drivers for high healthcare costs in patients with asthma and lead to higher expenses in patients with severe asthma [33], but a study with 333 asthma patients showed that indirect costs are also highly relevant when assessing the economic burden of asthma and that at all levels of disease severity indirect costs were twice as high as direct costs [32]. Especially in young adults, a diagnosis of asthma also means a substantial individual financial burden mainly driven by loss of income rather than direct healthcare costs [34]. Therefore, achieving asthma control in patients with severe asthma by treatment with IL-5/IL-5R α antibodies could potentially attenuate both individual and societal losses. Needless to say, anti-IL-5/ anti-IL-5R α therapy is associated with high treatment costs and the vigorous debate whether treatment with biologicals in severe asthma is cost-effective is ongoing. Numerous studies have analysed the cost-effectiveness of all approved antibodies and results are highly ambiguous, mainly due to different study designs and the variety of factors influencing direct and indirect costs [35–38]. Convincing evidence exists to the effect that biological treatment should be initiated when inhaled treatment is not sufficient to control disease and this includes conscientious assessment of inhaler adherence, because this is well known to be in need of improvement [39–41]. Concerning anti-IL-5/anti-IL-5R α therapy, treatment with benralizumab and mepolizumab potentially represents a cost-effective treatment option by reducing exacerbations and medication use and increasing overall disease control, especially when considering the reduced indirect treatment costs [42, 43]. However, further studies considering all cost-driving aspects and including positive influences on indirect cost, such as the loss of work productivity, are needed to make a definite point concerning cost-effectiveness. Further research should also include predictors for treatment response to antibodies. With regard to the steadily increasing number of biologicals approved for severe asthma, the choice of the right antibody for the right patient becomes increasingly difficult, but represents an important aspect in optimising treatment and thereby cost-effectiveness [44-46].

This study is limited by the small number of patients included and by missing data. Owing to the worldwide COVID-19 pandemic, many patients did not attend follow-up appointments and subsequently questionnaires were not filled out. No conclusions concerning the effects of antibodies other than mepolizumab and benralizumab can be drawn from the data, because only patients with IL-5/IL-5R α antibody treatment were included. The effect of responder status could not be assessed owing to the low number of patients. Furthermore, parts of the used questionnaire have not been validated.

In summary, IL-5/IL-5R α antibodies are highly effective in daily clinical practice and, by improving asthma control and QoL, can further lead to improved work productivity and less absenteeism at work. Self-reported work productivity significantly improved after 12 months of treatment and patients stated substantially fewer negative effects on their working situation.

Provenance: Submitted article, peer reviewed.

Acknowledgements: We thank all patients for their kind participation in the study.

Ethics statement: The study was approved by the local institutional review board of Hannover Medical School (number 8050_BO_K_2018).

Author contributions: N. Drick, H. Suhling, T. Welte and J. Fuge conceived the study; L. Brinkmann and H. Suhling performed data abstraction; L. Brinkmann performed data analysis; J. Fuge supervised the analysis and assisted with data interpretation; L. Brinkmann and N. Drick drafted the manuscript; and all authors contributed to the final version of the manuscript. N. Drick is the guarantor of the study. T. Welte passed away on 10 March 2024 after contributing to the present study.

Conflict of interest: L. Brinkmann has no relevant conflicts of interest. J. Fuge reports speaker fees from AstraZeneca. T. Welte reported personal fees from AstraZeneca, GSK and Sanofi Aventis, and his institution received research grants from the German Ministry of Research and Education. H. Suhling reports speaker fees from AstraZeneca, GSK and Novartis. N. Drick reports speaker fees for AstraZeneca.

Support statement: The study was funded as externally sponsored scientific research by AstraZeneca (ESR-18–14074). Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2023. Available from: http://ginasthma.org/

- 2 Hyland ME, Whalley B, Jones RC, *et al.* A qualitative study of the impact of severe asthma and its treatment showing that treatment burden is neglected in existing asthma assessment scales. *Qual Life Res* 2015; 24: 631–639.
- 3 Gruffydd-Jones K, Thomas M, Roman-Rodríguez M, *et al.* Asthma impacts on workplace productivity in employed patients who are symptomatic despite background therapy: a multinational survey. *J Asthma Allergy* 2019; 12: 183–194.
- 4 Ding B, Chen S, Srivastava D, *et al.* Symptom burden, health status, and productivity in patients with uncontrolled and controlled severe asthma in NOVELTY. *J Asthma Allergy* 2023; 16: 611–624.
- 5 Burnette A, Wang Y, Rane PB, *et al.* Incremental cost burden among patients with severe uncontrolled asthma in the United States. *J Manag Care Spec Pharm* 2023; 29: 825–834.
- 6 Pavord ID, Korn S, Howarth P, *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; 380: 651–659.
- 7 Bjermer L, Lemiere C, Maspero J, *et al.* Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels. *Chest* 2016; 150: 789–798.
- 8 Nair P, Wenzel S, Rabe KF, *et al.* Oral glucocorticoid–sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017; 376: 2448–2458.
- 9 Wenzel S, Ford L, Pearlman D, *et al.* Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013; 368: 2455–2466.
- 10 Busse W, Corren J, Lanier BQ, *et al.* Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001; 108: 184–190.
- 11 Menzies-Gow A, Corren J, Bourdin A, *et al.* Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med* 2021; 384: 1800–1809.
- 12 Albers FC, Bratton DJ, Gunsoy NB, *et al.* Mepolizumab improves work productivity, activity limitation, symptoms, and rescue medication use in severe eosinophilic asthma. *Clin Respir J* 2022; 16: 252–258.
- 13 Drick N, Brinkmann L, Fuge J, *et al.* Influence of anti-interleukin (IL)-5/anti-IL-5 receptor- α treatment on work productivity in patients with severe eosinophilic asthma. *ERJ Open Res* 2023; 9: 00665-2022.
- 14 Chung KF, Wenzel SE, Brozek JL, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343–373.
- **15** Milger K, Skowasch D, Hamelmann E, *et al.* Bronchodilator reversibility in the GAN severe asthma cohort. *J Investig Allergy Clin Immunol* 2022; 33: 446–456.
- 16 Lommatzsch M, Brusselle GG, Canonica GW, *et al.* Disease-modifying anti-asthmatic drugs. *Lancet* 2022; 399: 1664–1668.
- 17 Chen H, Blanc PD, Hayden ML, *et al.* Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. *Value Health* 2008; 11: 231–239.
- 18 Van Der Valk JPM, Hekking PP, Rauh SP, *et al.* Anti-IL-5/5Ra biologics improve work productivity and activity in severe asthma: a RAPSODI registry-based cohort study. *J Asthma* 2023; 60: 1869–1876.
- **19** Wu JJ, Lin C, Sun L, *et al.* Minimal clinically important difference (MCID) for Work Productivity and Activity Impairment (WPAI) questionnaire in psoriasis patients. *J Eur Acad Dermatol Venereol* 2019; 33: 318–324.
- 20 Plank PM, Hinze CA, Campbell V, *et al.* Relationship between the response to antibody therapy and symptoms of depression and anxiety disorders in patients with severe asthma. *J Asthma Allergy* 2023; 16: 421–431.
- 21 Moullec G, FitzGerald JM, Rousseau R, *et al.* Interaction effect of psychological distress and asthma control on productivity loss? *Eur Respir J* 2015; 45: 1557–1565.
- 22 Hakola R, Kauppi P, Leino T, *et al.* Persistent asthma, comorbid conditions and the risk of work disability: a prospective cohort study. *Allergy* 2011; 66: 1598–1603.
- 23 McDonald VM, Hiles SA, Godbout K, *et al.* Treatable traits can be identified in a severe asthma registry and predict future exacerbations. *Respirology* 2019; 24: 37–47.
- 24 Stubbs MA, Clark VL, Gibson PG, *et al.* Associations of symptoms of anxiety and depression with health-status, asthma control, dyspnoea, dysfunction breathing and obesity in people with severe asthma. *Respir Res* 2022; 23: 341.
- 25 Moore WC, Meyers DA, Wenzel SE, *et al.* Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010; 181: 315–323.
- 26 Yelin E, Katz P, Balmes J, *et al.* Work life of persons with asthma, rhinitis, and COPD: a study using a national, population-based sample. *J Occup Med Toxicol* 2006; 1: 2.
- 27 Taponen S, Lehtimäki L, Karvala K, *et al.* Correlates of employment status in individuals with asthma: a cross-sectional survey. *J Occup Med Toxicol* 2017; 12: 19.
- 28 Shim J, Jones GT, Pathan EMI, *et al.* Impact of biological therapy on work outcomes in patients with axial spondyloarthritis: results from the British Society for Rheumatology Biologics Register (BSRBR-AS) and meta-analysis. *Ann Rheum Dis* 2018; 77: 1578–1584.

- 29 Macfarlane GJ, Jones GT, Shim J. Are work outcomes improved in axial spondyloarthritis (axSpA) patients with biologic therapy? Results from the British Society for Rheumatology Register. *Arthritis Rheumatol* 2017; 69: Suppl. 10, 2144–2150.
- 30 Keat AC, Gaffney K, Gilbert AK, *et al.* Influence of biologic therapy on return to work in people with work disability due to ankylosing spondylitis. *Rheumatology* 2007; 47: 481–483.
- **31** Jansson SA, Backman H, Andersson M, *et al.* Severe asthma is related to high societal costs and decreased health related quality of life. *Respir Med* 2020; 162: 105860.
- 32 Serra-Batlles J, Plaza V, Morejon E, *et al.* Costs of asthma according to the degree of severity. *Eur Respir J* 1998; 12: 1322–1326.
- 33 Ivanova JI, Bergman R, Birnbaum HG, et al. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. J Allergy Clin Immunol 2012; 129: 1229–1235.
- 34 Håkansson KEJ, Løkke A, Ibsen R, *et al.* Beyond direct costs: individual and societal financial burden of asthma in young adults in a Danish nationwide study. *BMJ Open Respir Res* 2023; 10: e001437.
- 35 Alves S, Rufo JC, Crispim J. Economic evaluation of biological treatments in patients with severe asthma: a systematic review. *Expert Rev Pharmacoecon Outcomes Res* 2023; 23: 733–747.
- **36** Domínguez-Ortega J, Phillips-Anglés E, Barranco P, *et al.* Cost-effectiveness of asthma therapy: a comprehensive review. *J Asthma* 2015; 52: 529–537.
- 37 Wu AC, Paltiel AD, Kuntz KM, *et al.* Cost-effectiveness of omalizumab in adults with severe asthma: results from the Asthma Policy Model. *J Allergy Clin Immunol* 2007; 120: 1146–1152.
- 38 Brown R, Turk F, Dale P, et al. Cost-effectiveness of omalizumab in patients with severe persistent allergic asthma. Allergy 2007; 62: 149–153.
- **39** Engelkes M, Janssens HM, De Jongste JC, *et al.* Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J* 2015; 45: 396–407.
- 40 Bourdin A, Halimi L, Vachier I, et al. Adherence in severe asthma. Clin Exp Allergy 2012; 42: 1566–1574.
- **41** Rodriguez-Martinez CE, Sossa-Briceño MP, Castro-Rodriguez JA. Cost effectiveness of pharmacological treatments for asthma: a systematic review. *PharmacoEconomics* 2018; 36: 1165–1200.
- 42 Andersson M, Janson C, Kristensen T, *et al.* Cost effectiveness of benralizumab for severe, uncontrolled oral corticosteroid–dependent asthma in Sweden. *J Med Econ* 2020; 23: 877–884.
- 43 Padilla-Galo A, García-Ruiz AJ, Levy Abitbol RC, *et al.* Real-life cost-effectiveness of benralizumab in patients with severe asthma. *Respir Res* 2021; 22: 163.
- 44 Whittington MD, McQueen RB, Ollendorf DA, *et al.* Assessing the value of mepolizumab for severe eosinophilic asthma: a cost-effectiveness analysis. *Ann Allergy Asthma Immunol* 2017; 118: 220–225.
- 45 Chen W, Reddel HK, FitzGerald JM, *et al.* Can we predict who will benefit most from biologics in severe asthma? A *post hoc* analysis of two phase 3 trials. *Respir Res* 2023; 24: 120.
- 46 Kroes JA, Zielhuis SW, Van Roon EN, *et al.* Prediction of response to biological treatment with monoclonal antibodies in severe asthma. *Biochem Pharmacol* 2020; 179: 113978.