Anti-IL-5/5Ra biologics improve work productivity and activity in severe asthma: a RAPSODI registry-based cohort study

Valk, J.P.M. van der; Hekking, P.P.; Rauh, S.P.; Patberg, K.W.; Veen, I.A. van; Huisstede, A. van; ... ; RAPSODI Team

JOURNAL OF ASTHMA
2023, VOL. 60, NO. 10, 1869–1876
https://doi.org/10.1080/02770903.2023.2196563

Anti-IL-5/5Ra biologics improve work productivity and activity in severe asthma: a RAPSODI registry-based cohort study

J. P. M. van der Valk, MD, PhD[a], P. P. Hekking, MD, PhD[a], S. P. Rauh, PhD[b], K. W. Patberg, MD, PhD[c], I. A. van Veen, MD, PhD[d], A. Van Huisstede, MD, PhD[e], F. W. J. M. Smeenk, MD, PhD[f], M. J. T. van de Ven, MD, PhD[g], M. E. A. C. Broeders, MD, PhD[h], B. Hilvering, MD, PhD[i], J. van Exsel, MD[j], K. T. M. Oud, MD[k], B. Langeveld, MD, PhD[l], K. B. Fieten, MSc, PhD[m], A. van Veen, MD[n], S. Hashimoto, MD, PhD[i], J. K. Sont, PhD[o], A. ten Brinke, MD, PhD[p], and G. J. Braunstahl, MD, PhD[a,q]; on behalf of the RAPSODI Team

[a]Department of Pulmonary Medicine, STZ Center of Excellence for Asthma and COPD, Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands; [b]Department of Science, Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands; [c]Department of Pulmonary Medicine, Isala, Zwolle, The Netherlands; [d]Department of Pulmonary Medicine, Medical Center Twente, The Netherlands; [e]Northwest Clinics, Alkmaar, The Netherlands; [f]Department of Pulmonary Medicine, Catharina Hospital, Eindhoven, The Netherlands; [g]Department of Pulmonary Medicine, Rijnstate, Arnhem, The Netherlands; [h]Department of Pulmonary Medicine, Jeroen Bosch Hospital's, Hertogenbosch, The Netherlands; [i]Department of Pulmonary Medicine, Amsterdam UMC, Location University of Amsterdam, Amsterdam, The Netherlands; [j]Department of Pulmonary Medicine, Haga Hospital, The Hague, The Netherlands; [k]Department of Pulmonary Medicine, Hospital Gelderse Vallei, Ede, The Netherlands; [l]Department of Pulmonary Medicine, Deventer Hospital, Deventer, The Netherlands; [m]Dutch Asthma Center Davos, Davos, Switzerland; [n]Department of Pulmonary Medicine, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands; [o]Department of Biomedical Data Science, Medical Decision Making, Leiden University Medical Center, Leiden, The Netherlands; [p]Department of Pulmonary Medicine, Medical Center Leeuwarden, Leeuwarden, The Netherland; [q]Department of Pulmonary Medicine, Erasmus MC, Rotterdam, The Netherlands

ABSTRACT

Introduction: Severe asthma is associated with a serious disease burden, partially caused by limitations in activity and work impairment.

Aims and objectives: This study aims to relate treatment with biologics targeting IL-5/5Ra to work productivity and activity in the long term in a real-world context.

Material and methods: This is a registry-based multi-center cohort study evaluating data from adults with severe eosinophilic asthma included in the Dutch Register of Adult Patients with Severe Asthma for Optimal DIsease management (RAPSODI). Patients that started with anti-IL-5/5Ra biologics and completed the work productivity and activity improvement questionnaire, were included. Study and patient characteristics were compared between the employed and unemployed patients. Work productivity and activity impairment are related to accompanying improvements in clinical outcomes.

Results: At baseline, 91 of 137 patients (66%) were employed which remained stable throughout the follow-up period. Patients in the working age category were younger and had significantly better asthma control ($p = 0.02$). Mean overall work impairment due to health decreased significantly from 25.5% (SD2.6) to 17.6% (SD 2.8) during 12 months anti-IL-5/5Ra biologics treatment ($P = 0.010$). There was a significant association between ACQ6 and overall work improvement after targeted therapy ($\beta = 8.7$, CI 2.1–15.4, $P = 0.01$). The improvement of asthma control of 0.5 points on the asthma Control Questionnaire was associated with an overall work impairment of −9%.

Conclusions: Work productivity and activity in severe eosinophilic asthma improved after starting anti-IL-5/5Ra biologics. Clinically relevant improvement in asthma control was associated with an overall work impairment score of −9% in this study.

Abbreviations: ACQ: Asthma Control Questionnaire; AD: atopic dermatitis; AQLQ: Asthma Quality of Life Questionnaire; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; MCID: minimal clinically important difference; RA: rheumatoid arthritis; RAPSODI: Register of Adult Patients with Severe Asthma for Optimal DIsease management; WPAI: work productivity and activity improvement

ARTICLE HISTORY

Received 6 March 2023
Revised 20 March 2023
Accepted 24 March 2023

KEYWORDS

Asthma; anti-IL-5/5Ra biologics; work productivity; activity; WPAI; MCID; AQLQ; ACQ6

CONTACT J. P. M. van der Valk h.kuiper-vandervalk@franciscus.nl Department of Pulmonary Medicine, STZ Center of Excellence for Asthma and COPD, Franciscus Gasthuis & Vlietland, P.O. Box 3045 PM, Rotterdam, The Netherlands.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/02770903.2023.2196563.

Introduction

Severe asthma is defined as an uncontrolled disease despite adequate assessment of aggravating factors and adherence to therapy with medium-high dose inhaled steroids and a second controller, or that needs maintenance oral corticosteroids to control the disease (1). It is associated with a high disease burden, partially caused by limitations in activity and work impairment (2,3). Approximately three-quarters of asthma patients reported the disease burden as influencing their work productivity (3,4). Better asthma control might contribute to less absenteeism and increased work and daily life activity. Work positively affects health by improving daily structure, self-esteem, self-development, and social contacts and offers financial security (5), and is therefore an important outcome from a patient perspective.

Patients with severe eosinophilic asthma are eligible for additional treatment with biologics targeting the IL-5 pathway (i.e., mepolizumab, reslizumab, and benralizumab), which has a proven positive effect on exacerbation rates, lung function, need for oral corticosteroids and quality of life (6,7). In highly selected participants in phase 3 trials, anti-IL5 treatment has been shown to improve work productivity and activity (8). The health-related quality of life and work productivity is greater among patients treated with add-on biologics compared to patients treated with high-dose inhalation corticosteroids alone or systemic corticosteroids (4). However, whether and to what extent work productivity and activity improve after initiation of therapy with anti-IL-5/5Ra biologics in a real-world context is largely unknown.

In this study, we compare patient characteristics of employed- and unemployed severe asthma patients starting with anti-IL-5/5Ra biologics. Moreover, work productivity and activity impairment are measured by the WPAI questionnaire (baseline) and followed up for 12 months.

In addition, we will investigate whether baseline characteristics can predict improvement in work productivity and whether improvements in work productivity and activity impairment are related to accompanying improvements in clinical outcomes after therapy with anti-IL-5/5Ra biologics. The last objective is to determine the association between the Minimal Clinically Important Difference (MCID) for asthma control of 0.5 points and the percentage decrease in overall work impairment.

Material and methods

Design and study the population

This is a registry-based multi-center cohort study evaluating data from adults with severe eosinophilic asthma included in the Dutch Registry of Adult Patients with Severe Asthma for Optimal DIsease management (RAPSODI) between April 2016 and March 2021 (9,10). We retrieved data from individuals with severe asthma from 13 Dutch hospitals from the RAPSODI registry, which is based on two sources: annual electronic case report forms (eCRFs) (CASTOR EDC platform, Amsterdam, The Netherlands) and 3-monthly electronic patient questionnaires (PatientCoach, Leiden University Medical Center, Leiden, The Netherlands) (10). Patients in the working age category (18–67 years) that started with anti-IL-5/5Ra biologics (i.e., mepolizumab, reslizumab, or benralizumab) and completed the work productivity and activity improvement questionnaire (WPAI General Health) within 2 months after the start of anti-IL-5/5Ra treatment and at least one time during follow-up (12 months), were included. Patients aged 18–67 years were considered to be in the working age category because 67 years is the official age of retirement in the Netherlands. Patient characteristics were retrieved from the RAPSODI registry database (i.e., age, BMI, sex and FEV_1). Each hospital contributed to registering data for eligible patients who provide written informed consent.

Questionnaires

Patients included in RAPSODI were asked to complete the ACQ6, AQLQ and WPAI questionnaires every 3 months voluntarily. The ACQ6 is a simple-validated questionnaire (6 items) that measures (change in) asthma control, which occurs spontaneously or as a result of treatment. A score of <0,75 is controlled-, ≥0,75 and <1,5 is partially controlled-, and ≥1,5 is uncontrolled disease. The MCID of the ACQ6 is 0.5 points (11). The AQLQ is a disease-specific health-related quality-of-life instrument that measures both; the physical and emotional impact of asthma. The MCID of the AQLQ is also 0.5 points (12). The WPAI questionnaire is an instrument to measure impairments in work and activity (13). WPAI outcomes were expressed as impairment percentages, with higher percentages indicating greater impairment (i.e., less productivity and activity). The WPAI (General Health) questionnaire contains 6 questions: Q1) currently employed, Q2) hours missed due to health problems, Q3) hours missed due to other reasons, Q4) hours actually worked, Q5) degree of health affected productivity while working and Q6) degree of health affected regular activities (14).

Statistical analysis

Patient and study characteristics were reported in percentages, means, and standard deviation. Patient

and study characteristics of patients with anti-IL-5/5Ra biologics with and without WPAI score were compared with an independent *T*-test and Chi-squared test. The same applies to patient and study characteristics of employed- and unemployed patients.

A linear mixed model was used to compare WPAI scores over time in 4 models: 1) as a percentage of overall work impairment due to health; 2) as a percentage of impairment while working due to health; 3) as a percentage of work time missed due to health; 4) and as a percentage activity impairment due to health scores over time. In the mixed models, time was considered as a fixed effect and a random intercept on the patient level was included to account for the dependency of the repeated observations within the patient.

Linear regression analysis was used to determine if baseline characteristics such as age, sex, and BMI were predictors of change in overall work impairment due to health between baseline and 12-month follow-up. Linear regression was also used to determine if improvement of FEV_1, ACQ6-score, and AQLQ-score were associated with overall work productivity improvement 12 months after anti-IL-5/5Ra biologic treatment.

If there is a significant association between overall impairment and improvement of ACQ6, the association between the MCID for asthma control of 0.5 points and percentages of overall work impairment will be determined (15,16). A p values of 0.05 is considered significant. Statistical analyses were performed with SPSS version 27.

Results

Inclusion

In total 1165 patients were included in the RAPSODI registry (date 01/03/2022) of which 725 were treated with anti-IL-5/5Ra biologics (Figure 1). Of these patients, 170 completed the WPAI within 2 months after the start of anti-IL-5/5Ra treatment and at least one time during follow-up (12 months). Eighty-one percent ($N = 137$) belonged to the working age category and were analyzed. Of these 137 patients, 91 patients were employed.

Patient and study characteristics of patients with- and without WPAI score

The patients who were treated with anti-IL-5/5Ra and completed the WPAI score were significantly younger compared to the group treated with anti-IL-5/5Ra and didn't complete the WPAI score (53.2 versus 57.5 years, $P < 0.001$). The percentage of men and mean BMI, ACQ6, AQLQ, and FEV_1 did not significantly differ between these groups.

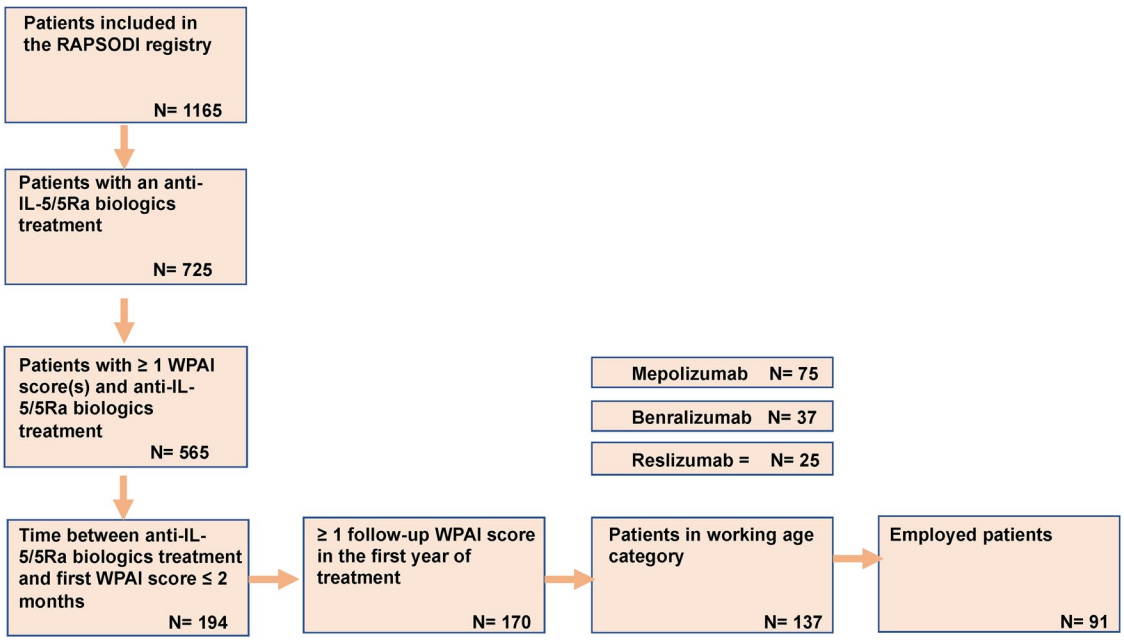

Figure 1. Flowchart of patient selection.
This flowchart demonstrates patient inclusion. Patients were selected on anti-IL-5/5Ra biologic treatment (mepolizumab, reslizumab or benralizumab) and completed the WPAI questionnaire within 2 months and at least one WPAI score during 12 months of follow-up. More than half of the patients was employed at the start of anti-IL-5/5Ra biologic treatment.

Patient and study characteristics of employed- and unemployed patients

Of the 137 analyzed patients, 91 patients were employed and 46 were unemployed. There were more men in the employed group compared to the unemployed group, although this difference was not statistically significant (58.2% versus 48.9%, $P = 0.30$). Compared to unemployed patients, employed patients were younger (51.3 versus 54.8 years, $P = 0.07$) and had a lower BMI (27.8 versus 29.3, $p = 0.25$), however, not significantly different. The FEV_1 and asthma quality of life (AQLQ) favored employed patients; 2.7 liters versus 2.4 liters and 5.4 versus 4.8 points, respectively, however, also not significantly different. The asthma control (ACQ6) was significantly better (1.8 versus 2.3 points, p values 0.02) for the employed patients compared to the unemployed patients.

In Table 1, the baseline study and patient characteristics were reported for all patients treated with anti-IL-5/5Ra biologics ($N = 725$), the subgroup that completed the WPAI forms ($N = 137$), and the employed- ($N = 91$) and unemployed patients separately ($N = 46$).

Anti-IL-5/5Ra treatment and work productivity

Of the analyzed group ($n = 137$), 55% was treated with mepolizumab, 27% with benralizumab, and 18% with reslizumab. At baseline, 91 (66%) patients were employed which remained stable throughout the follow-up period (68%, 69%, and 62% after 2–4, 4–8 and 8–12 months, respectively). So the percentage of employed patients did not increase during targeted treatment.

Work productivity and activity during anti-IL-5/5Ra biologics

For employed patients, the mean overall work impairment due to health decreased significantly from 25.5% (SD2.6) to 17.6% (SD2.8) after 12 months of anti-IL-5/5Ra treatment ($P = 0.010$). Similar results applied for mean impairment while working due to health: 32.8% (SD3.1) to 21.2% (SD3.3), $P = 0.006$) and work time missed due to health; 18.1% (SD3.3) to 7.8% (SD2.6), ($P = 0.048$). For employed and unemployed patients, the mean activity impairment due to health decreased significantly (50.5% (SD 2.6) to 32.4% (SD2.9), ($P < 0.001$). These results are shown in Table 2.

Possible baseline characteristics as predictors of improvement in work productivity

Age, sex, and BMI do not predict change in overall work impairment due to health (age: $\beta = 0.3$, CI −0.4–0.9, $P = 0.46$, sex: $\beta = -2.8$, CI −15.5–9.8, $P = 0.66$, BMI: $\beta = 0.1$, CI −1.2–1.5, $P = 0.85$) between baseline and after 12 months anti-IL-5/5Ra biologics treatment.

Association between improvements in work productivity impairment and clinical outcomes

There was a significant association between improvement in ACQ6 and change in overall work impairment after 12 months anti-IL-5/5Ra biologic treatment ($\beta = 8.7$, CI 2.1–15.4, $P = 0.01$). This did not apply to the improvement of AQLQ and FEV_1 (Table 3).

Minimal clinically important difference (MCID) for ACQ6 and the associated percentage overall work impairment

To determine the association between the ACQ6 scores and WPAI scores (domain overall work impairment), these scores per patient are shown in a scatterplot (Figure 2). Every dot represents a patient, who completed both questionnaires. Linear regression has been used to determine the trendline between these

Table 1. Baseline characteristics of study population derived from RAPSODI database.

Characteristics	All patients with anti-IL-5/5Ra biologics $N = 725$	Patients with anti-IL-5/5Ra biologics and WPAI scores $N = 137$	*P*-value*	Employed Patients $N = 91$	Not employed patients $N = 46$	*P*-value
Age, years, mean (SD)	57.5 (13.4) $N = 723$	53.2 (9.8) $N = 137$	<0.001	51.3 (9.4) $N = 91$	54.8 (11.5) $N = 46$	0.07
Male sex, %	49.4 $N = 725$	55.5 $N = 137$	0.11	58.2 $N = 91$	48.9 $N = 45$	0.30
BMI Kg/m2, mean (SD)	27.8 (5.4) $N = 724$	28.4 (4.8) $N = 137$	0.20	27.8 (4.7) $N = 91$	29.3 (5.2) $N = 46$	0.25
ACQ6 score, mean (SD)	1.7 (1.1) $N = 650$	2.0 (1.0) $N = 137$	0.10	1.8 (0.9) $N = 91$	2.3 (1.2) $N = 46$	0.02
AQLQ score mean (SD)	5.3 (1.1) $N = 626$	5.4 (1.1) $N = 110$	0.65	5.4 (1.0) $N = 73$	4.8 (1.0) $N = 37$	0.61
FEV_1 in L, mean (SD)	2.5 (0.9) $N = 653$	2.6 (0.9) $N = 131$	0.60	2.7 (0.8) $N = 89$	2.4 (0.8) $N = 44$	0.56

BMI: Body mass index, ACQ6: Asthma control questionnaire, AQLQ: Asthma Quality of Life, FEV1: Forced Expiratory Volume in 1 s.
*Patients with anti-IL-5/5Ra biologics without WPAI score ($N = 588$ (725–137)) compared with patients with anti-IL-5/5Ra biologics and WPAI scores ($N = 137$).

Table 2. Mixed model outcomes of the WPAI questionnaire overtime on the domain overall work impairment due to health, impairment while working due to health and work time missed due to health ($N = 91$) and the domain activity impairment due to health ($N = 137$).

Crude model	*N*	Estimate (%)	95% CI	*P*-value overall model	Compared to baseline		
					Estimate (%)	95% CI	*P*-value
Overall work impairment due to health				0.010			
Baseline	88	25.5	20.4–30.6				
2–4 months	66	18.4	12.9–23.9		−7.1	−13.1 – −1.1	0.020
4–8 months	72	21.8	16.4–27.2		−3.7	−10.0 –2.5	0.237
8–12 months	69	17.6	11.9–23.2		−7.9	−13.5 – −2.4	0.006
Impairment while working due to health				0.006			
Baseline	81	32.8	26.6–38.9				
2–4 months	59	25.0	17.5–32.6		−7.7	−15.3 – −.22	0.044
4–8 months	70	25.0	18.9–31.1		−7.8	−14.9 – −.55	0.035
8–12 months	66	21.2	14.6–27.8		−11.5	−17.9 – −5.2	<0.0.01
Work time missed due to health				0.048			
Baseline	92	18.1	11.6–24.6				
2–4 months	81	15.8	8.5–23.2		−2.2	−7.8 –3.3	0.423
4–8 months	61	11.2	5.7–16.8		−6.9	−12.5 – −1.2	0.019
8–12 months	57	7.8	2.6–13.0		−10.3	−18.5 – −2.1	0.014
Activity impairment due to health				<0.001			
Baseline	136	50.5	45.5–55.6				
2–4 months	103	33.9	27.9–39.9		−16.6	−22.4 – −10.7	<0.001
4–8 months	121	34.7	29.3–40.1		−15.8	−21.3 – −10.4	<0.001
8–12 months	109	32.4	26.7–38.2		−18.1	−23.8 – −12.4	<0.001

Table 3. Univariate linear regression of possible associated variables with change in overall work impairment over time (baseline vs 12 months follow-up) ($N = 91$).

Variables	B	95%CI	*P*-value
ΔACQ6*	8.7	2.1–15.4	0.01
ΔAQLQ*	−2.2	−10.5–6.2	0.61
ΔFEV_1 in L*	−4.2	−16.6–8.3	0.51

*Change in ACQ6, AQLQ, and FEV1 between baseline and after 12 months of follow-up.

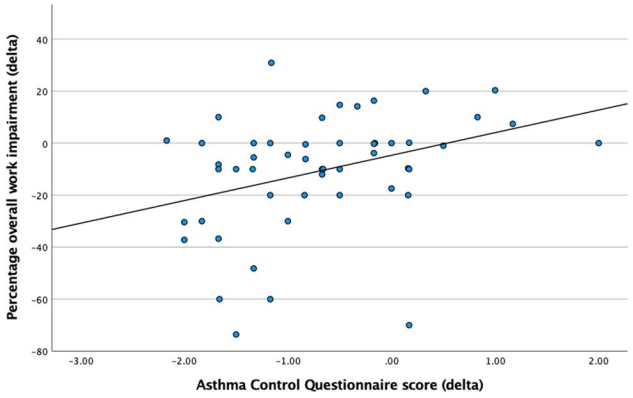

Figure 2. The equivalent MCID for the overall work impairment.

The ACQ6 scores and WPAI scores per patient are shown in this scatterplot. Every dot represents a patient, who completed both questionnaires. Linear regression has been used to determine the association between these two scores. The standard MCID of ACQ6 is −0.5 points and is associated with an overall work impairment of −9.0 percent using the regression formula ($Y = -4.68 + 8.7 * x$; with $x = -0.5$).

two scores and has been plotted in the same figure. The standard MCID of ACQ6 is 0.5 points. Using this trendline results in percentages for the overall work impairment of 9.0% ($Y = -4.68 + 8.7 * x$; with $x = -0.5$).

Discussion

Treatment with anti-IL-5/5Ra biologics significantly improved work productivity and activity in working patients in all domains in our study. Work productivity and activity mainly increased in the first months after starting anti-IL5 therapy and stabilized over time. A difference in WPAI score of approximately 9%, based on the MCID of ACQ6 seems to be clinically relevant in this population. More than half of the patients was employed at the initiation of anti-IL-5/5Ra treatment and after 12 months of follow-up. There were more men in the employed group, the patients in the employed group were slightly younger, had a lower BMI, and had a higher FEV_1. So these traits seem to be beneficial for a better work capacity. Employed patients had better asthma control than unemployed patients, supporting the need to control the disease first before being able to perform work. Our study found a significant association between ACQ6 and overall work impairment over time.

The work productivity and activity increase in working patients treated with anti-IL-5/5Ra biologics is in line with the findings in two randomized, placebo-controlled trials investigating the effect of mepolizumab on the activity limitation and work productivity of asthma patients (7,17). An observational study with 1109 asthma patients showed that patients receiving biologics (vs maintenance systemic corticosteroids, high-dosage inhaled corticosteroids with additional controllers) had lower work impairment (17% vs 34%, 27%, respectively) (4). The positive

effect of systemic treatment on work-related outcomes in employed patients with other chronic physical disabilities is also previously demonstrated by Behrens et al. showing a strong association between TNF-blocker (Adalimumab) and improvements in work-related outcomes in 783 employed patients with rheumatoid arthritis (RA) during 24 months of treatment (18). Similarly, a study in Atopic Dermatitis (AD) demonstrated that work impairment decreased significantly from baseline (35.5%) to week 52 (11.5%) in 218 adult patients with moderate-to-severe AD treated with Dupilumab (19).

An overall work impairment of 9% seems to be clinically relevant in this population if you associate this with the MCID of 0.5 points of the ACQ6. The clinically relevant productivity loss of WPAI was estimated to be 20% in patients with psoriasis (Psoriasis Area and Severity Index) (20). The estimates in this study were based on 12-week treatment outcomes. The clinical relevance needs to be estimated for longer periods to understand the full impact of clinical improvement on WPAI. In our study, we have a follow-up period of 12 months. So a percentage of 9% seems more robust and clinically relevant in this population for this time interval, however, this should be validated in future studies.

More than half of the patients was employed at the initiation of anti-IL-5/5Ra biologics which is in line with rates found in patients with other physical, sensory, psychological, and intellectual disabilities (60%) (21). However, this is substantially lower compared to the rate of employment in people without chronic disease (82%) (21).

The better the asthma control, the higher the work productivity of the asthma patients in our study. Sadatsafavi et al. demonstrated that work productivity loss was associated with asthma control (22). A cohort study in patients with moderate-to-severe persistent allergic asthma ($N = 7709$) found a reduction in asthma-related work, school, and activity impairment associated with better asthma control (23). A previously performed study by Lee et al. showed a significant relationship between asthma control and its impact on healthcare resource utilization, costs, work productivity and health-related quality of life (3). This is in line with the study of Hiles et al. This study demonstrated that work productivity and impairment in daily activity were more frequently reported in severe asthma and in participants with worse asthma control, impaired lung function and more past-year exacerbations ($P < 0.01$) (24). In contrast, the FEV_1 and AQLQ in our study were not associated with overall work impairment over time. For AQLQ this may be due to the limited number of completed AQLQ questionnaires and for FEV_1 due to the minimal improvement in FEV_1 after 12 months.

A unique set of real-life data with multiple evaluation moments (questionnaires) is used in this multi-center study. Selection bias seems unlikely because our results are similar to the clinical trials. Limitations of this study comprise the number of patients included in this study by the limited number of completed WPAI questionnaires. Furthermore, due to the retrospective nature of this study, there is no control group and there are missing data.

Despite these shortcomings, it seems very clear that early-stage systemic treatment in patients with chronic physical disabilities who belong to the working category may reduce the disease burden for the individual, increase work productivity and is likely to have positive social-economic effects on society.

Our findings suggest that getting back to work is difficult for patients with severe asthma despite initiating targeted treatment. However, anti-IL-5/5Ra biologics improve the ability to work and be active in patients who are already working. A decrease in WPAI score of ≥ 9% was associated with an improvement in ACQ6 score of ≥ 0,5 and seems to be clinically relevant. Therefore, early-stage treatment with anti-IL-5/5Ra biologics in patients with severe asthma who belong to the working category may reduce the disease burden for the individual and is likely to have positive social-economic effects on society.

Acknowledgements

The authors acknowledge the patients for their participation and the RAPSODI teams (supplementary material 1). Written informed consent was obtained from all patients.

Authors' contributions

Dr. J.P.M. van der Valk is the main author and contributed to data analysis. Dr. P.P. Hekking involved in data analysis support and drafting the manuscript. Dr. S.P. Rauh contributed to statistical analyses. Dr. G.J. Braunstahl is the supervisor and involved in drafting the manuscript. J.K. Sont involved in design of the RAPSODI registry and data collection. Rapsodi team provided support as co-authors.

Declaration of interest

The authors declare no conflict of interest.

Funding

RAPSODI is sponsored by Novartis, GlaxoSmithKline, Teva, AstraZeneca, and SanofiGenzyme.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

1. Available from: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf [last accessed 1 March 2020].
2. Gruffydd-Jones K, Thomas M, Roman-Rodríguez M, Infantino A, FitzGerald JM, Pavord I, Haddon JM, Elsasser U, Vogelberg C. Asthma impacts on workplace productivity in employed patients who are symptomatic despite background therapy: a multinational survey. J Asthma Allerg. 2019;12:183–194. doi:10.2147/JAA.S204278.
3. Lee LK, Ramakrishnan K, Safioti G, Ariely R, Schatz M. Asthma control is associated with economic outcomes, work productivity and health-related quality of life in patients with asthma. BMJ Open Respir Res. 2020;7(1):e000534. doi:10.1136/bmjresp-2019-000534.
4. Soong W, Chipps BE, O'Quinn S, Trevor J, Carr WW, Belton L, Trudo F, Ambrose CS. Health-related quality of life and productivity among US patients with severe asthma. J Asthma Allerg. 2021;14:713–725. doi:10.2147/JAA.S305513.
5. Satuf C, Monteiro S, Pereira H, Esgalhado G, Afonso RM, Loureiro M. The protective effect of job satisfaction in health, happiness, well-being and self-esteem. Int J Occup Saf Ergon. 2018;24(2):181–189. doi:10.1080/10803548.2016.1216365.
6. Gibson PG, Prazma CM, Chupp GL, Bradford ES, Forshag M, Mallett SA, Yancey SW, Smith SG, Bel EH. Mepolizumab improves clinical outcomes in patients with severe asthma and comorbid conditions. Respir Res. 2021;22(1):171. doi:10.1186/s12931-021-01746-4.
7. Agache I, Beltran J, Akdis C, Akdis M, Canelo-Aybar C, Canonica GW, Casale T, Chivato T, Corren J, Del Giacco S, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines – recommendations on the use of biologicals in severe asthma. Allergy. 2020;75(5):1023–1042. doi:10.1111/all.14221.
8. Albers FC, Bratton DJ, Gunsoy NB, Cockle SM, Alfonso-Cristancho R, Braunstahl GJ. Mepolizumab improves work productivity, activity limitation, symptoms, and rescue medication use in severe eosinophilic asthma. Clin Respir J. 2022;16(3):252–258. doi:10.1111/crj.13474.
9. Eger K, Kroes JA, ten Brinke A, Bel EH. Long-term therapy response to anti-IL-5 biologics in severe asthma—A real-life evaluation. J Allergy Clin Immunol Pract. 2021;9(3):1194–1200. doi:10.1016/j.jaip.2020.10.010.
10. Hashimoto S, Kroes JA, Eger KA, Mau Asam PF, Hofstee HB, Bendien SA, Braunstahl GJ, Broeders MEAC, Imming LM, Langeveld B, RAPSODI team, et al. Real-world effectiveness of reslizumab in patients with severe eosinophilic asthma – First initiators and switchers. J Allergy Clin Immunol Pract. 2022;10(8):2099–2108.e6. doi:10.1016/j.jaip.2022.04.014.
11. Korn S, Both J, Jung M, Hubner M, Taube C, Buhl R. Prospective evaluation of current asthma control using ACQ6 and ACT compared with GINA criteria. Ann Allergy Asthma Immunol. 2011;107(6):474–479.
12. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax. 1992;47(2):76–83.
13. Chen H, Blanc PD, Chawla A, Hayden M, Bleecker ER, Lee JH. Assessing productivity impairment in patients with severe or difficult-to-treat asthma: validation of the work productivity activity impairment – Asthma Questionnaire. J Allergy Clin Immunol. 2006;117(2):S181.
14. Meetinstrumentenzorg. Available from: https://meetinstrumentenzorg.nl/instrumenten/work-productivity-and-activity-impairment-questionnair [last accessed 7 November 2022.].
15. Bonini M, Di Paolo M, Bagnasco D, Baiardini I, Braido F, Caminati M, Carpagnano E, Contoli M, Corsico A, Del Giacco S, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. Eur. Respir Rev. 2020;29:190137.
16. Kon SSC, Canavan JL, Jones SE, Noalan CM, Clark AL, Dickson MJ, Haselden BM, Polkey M, Man WD-C. Minimum clinically important difference for COPD Assessment Test: a prospective analysis. Lancet Respir Med. 2014;2:195–203.
17. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, Trevor JL, Magnan A, Ten Brinke A. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med. 2017;5(5):390–400.
18. Behrens F, Tony HP, Koehm M, Schwaneck EC, Gnann H, Grerer G, Burkhardt H, Schmalzing M. Sustained improvement in work outcomes in employed patients with rheumatoid arthritis during 2 years of adalimumab therapy: an observational cohort study. Clin Rheumatol. 2020;39(9):2583–2592.
19. Ariëns LFM, Bakker DS, Spekhorst LS, Van der Schaft J, Thijs JL, Haeck I, Flinterman AE, Kamsteeg M, Schuttelaar MLA, De Bruin-Weller MS. Rapid and sustained effect of dupilumab on work productivity in patients with difficult-to-treat atopic dermatitis: results from the Dutch BioDay registry. Acta Derm Venereol. 2021;101(10):adv00573. doi:10.2340/00015555-3886.
20. Wu JJ, Lin C, Sun L, Goldblum O, Zbrozek A, Berge R, Augustin M, Feldman SR. Minimal clinically important difference (MCID) for work productivity and activity

impairment(WPIA) questionnaire in psoriasis patients. J Eur Acad Dermatol Venereal. 2019;33(2):318–324.
21. Meting IVRPH-indicatoren 2020. Available from: https://www.cbs.nl/nl-nl/maatwerk/2022/09/meting-ivrph-indicatoren-2020 [last accessed 12 September 2022].
22. Sadatsafavi M, Rousseau R, Chen W, Zhang W, Lynd L, FitzGerald JM. The preventable burden of productivity loss due to suboptimal asthma control: a population-based study. Chest. 2014;145(4):787–793.
23. Zazzali JL, Raimundo KP, Trzaskoma B, Rosén KE, Schatz M. Changes in asthma control, work productivity, and impairment with omalizumab: 5-year EXCELS study results. Allergy Asthma Proc. 2015;36(4):283–292.
24. Hiles SA, Harvey ES, McDonald WM, Peters M, Bardin P, Reynolds PN, Upham JW, Baraket M, Bhikoo Z, Bowden J, et al. Working while unwell: workplace impairment in people with severe asthma. Clin Exp Allergy. 2018;48(6):650–662.