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SHORT RESEARCH REPORT

Patient-reported outcome measures after 8 weeks of mepolizumab treatment and long-term outcomes in patients with severe asthma: an observational study

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Abstract

Background The novel anti-IL-5 drug mepolizumab improves asthma outcomes in the majority but not all patients with severe eosinophilic asthma. Currently it is difficult to predict an individuals' chance of being a responder. Early changes in patient-reported outcome measures may contribute to the prediction of long-term outcomes. *Aim* To compare early changes in patient-reported outcome measures after 8 weeks and long-term response to mepolizumab treatment. *Method* 22 severe eosinophilic asthma patients starting mepolizumab therapy in a severe asthma centre in the Netherlands were evaluated on baseline, 8 weeks and 52 weeks, collecting questionnaire scores and asthma-related parameters. Well-controlled asthma was defined as an asthma control questionnaire score ≤ 0.75. Long-term treatment response was defined as continuing mepolizumab therapy at 52 weeks. *Results* Nine patients (41%) had well-controlled asthma at 8 weeks and all were mepolizumab responders at 52 weeks (positive predictive value = 100%, 95%CI 66–100), versus only 5 responders out of 13 patients with not well-controlled asthma at 8 weeks (negative predictive value = 62%, 95%CI 32–86). *Conclusion* The results in this study suggest that patients receiving mepolizumab therapy with an ACQ-score ≤ 0.75 at 8 weeks are unlikely to need extensive monitoring, for they are very likely to be long-term responders.

Keywords Severe asthma · Mepolizumab · Biologics · Patient-reported outcome measures · Personalized medicine · Treatment evaluation

Impacts on practice

- Therapy evaluation of mepolizumab treatment based on PROMs could be expedited to as early as 8 weeks after treatment initiation.
- The findings in this study suggest the selection of patients requiring less extensive follow-up after initiating mepolizumab treatment.

Introduction

The novel anti-IL-5 drug mepolizumab improves asthma outcomes in the majority but not all patients with severe eosinophilic asthma [1]. Baseline patient characteristics may influence mepolizumab-induced outcomes, but currently it is difficult to predict an individuals' chance of being a responder to treatment with mepolizumab [2]. Frequently

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used patient-reported outcome measures (PROMs) in severe asthma care are the Asthma Control Questionnaire (ACQ) and the Asthma-related Quality of Life Questionnaire (AQLQ). A low ACQ-score indicates good asthma control, and a high AQLQ-score indicates better quality of life [3, 4]. Early changes in these PROMs may contribute to the prediction of long-term outcomes, as shown in a study on the prediction of asthma exacerbations [5]. We hypothesize that early changes in the ACQ and AQLQ are associated with long-term response to mepolizumab treatment for patients with severe asthma.

Aim

The aim of this study was to compare ACQ and AQLQ scores 8 weeks after starting mepolizumab for patients with or without long-term response to mepolizumab treatment. Furthermore, in patients who already achieved well-controlled asthma in week 8, we evaluated the chance of becoming a mepolizumab responder in week 52.

Ethics approval

Ethical approval was waived by the local Ethics Committee of the Medical Centre Leeuwarden in view of the retrospective nature of the study and all the performed procedures were part of the routine care.

Method

Severe eosinophilic asthma patients starting mepolizumab therapy in a severe asthma centre in the Netherlands were evaluated on baseline, 8 weeks and 52 weeks as part of regular care. Eosinophilic asthma was diagnosed according to GINA guidelines for severe asthma (ICD-10 code J82.83) [6]. All patients starting mepolizumab treatment in the inclusion period (January 2017 to August 2018) were selected for this study. Inhalation technique and adherence to inhalers were optimized before and during mepolizumab treatment. Spirometry, forced expiratory nitric oxide (FeNO), serum eosinophil count, daily oral corticosteroid dose (OCS), and questionnaires were recorded at each evaluation. Well-controlled asthma was defined as an ACQ $\leq$ 0.75 [7]. All patients used prednisolone as their maintenance OCS. Long-term treatment response was defined as continuing mepolizumab therapy at 52 weeks, based on the decision by the healthcare professionals. This decision was made using a predefined protocol, based on exacerbation rate, OCS use, lung function, and patient's well-being. All participants signed informed consent before participating in this study. Patients discontinuing mepolizumab treatment due to side effects and patients with missing questionnaire data at baseline, 8 weeks or 52 weeks were excluded from the study.

Continuous variables were expressed as medians (IQR) and categorical variables as numbers and percentages. Differences between subgroups were analysed using Mann–Whitney U, $\chi 2$, or Fisher exact tests when applicable. A p value < 0.05 indicated statistical significance. All statistical analyses were performed with IBM SPSS Statistics version 24.0.

Results

Twenty-five patients initiated mepolizumab in the study period. Two were excluded due to incomplete data, and 1 patient discontinued mepolizumab due to side effects. Baseline characteristics are described in Table 1.

Of the 22 included patients, 14 patients (64%) continued mepolizumab therapy at 52 weeks after initiation, classifying them as long-term responders. Patient characteristics are compared in Table 1. A statistically significant difference was found in OCS dose at baseline between non-responders and responders.

For the total study cohort, median ACQ score decreased from 2.33 (IQR 1.50–2.83) at baseline to 1.09 (IQR 0.67–1.70) after 8 weeks of therapy ($p < 0.001$) and median OCS dose decreased from 8.8 (IQR 2.5–10) to 5 mg/day (IQR 0–7.5) ($p = 0.004$). Median AQLQ score increased from 5.09 (IQR 4.20–5.36) to 5.82 (IQR 4.96–6.46) ($p < 0.001$). The asthma-related parameters for responders and non-responders are described in Table 2. At baseline, there was no statistically significant difference in ACQ and AQLQ for the long-term responders and non-responders, while at 8 weeks a statistically significant difference between responders and non-responders was found for both parameters (Fig. 1). The OCS dose, while different at baseline, did not differ at the 8 week mark.

Nine patients (41%) had well-controlled asthma at 8 weeks and were also mepolizumab responders at 52 weeks (positive predictive value = 100%, 95%CI 66–100), versus 5 responders out of 13 patients without well-controlled asthma at 8 weeks (negative predictive value = 62%, 95%CI 32–86). Consequently, the relative risk for being a responder at 52 weeks for patients with well-controlled asthma compared to the patients without well-controlled asthma at 8 weeks was 2.6 (95%CI 1.307–5.171; $p = 0.004$).

Discussion

In this explorative study in patients initiating mepolizumab therapy, we found a statistically significant difference in PROMs at 8 weeks between long-term responders and non-responders, whereas these did not differ at baseline.

Table 1 Baseline characteristics

Characteristic	Population (N = 22)		Non-responder (N = 8)		Responder (N = 14)		*p* value
Age (y)*	52	(46–61)	49	(37–61)	53	(49–61)	0.305
Gender; male, N (%)	11	(50)	5	(63)	6	(43)	0.659
Body mass index (kg/m^2)*	26.0	(24.3–28.6)	25.8	(24.5–31.6)	26.8	(23.9–28.6)	0.885
Former smoker, N (%)	10	(46)	4	(50)	6	(43)	1.000
Late onset asthma, N (%)	15	(68)	3	(38)	12	(86)	0.052
Non-atopic asthma, N (%)	17	(81)	7	(88)	10	(77)	1.000
OCS dose (mg/day)*	8.8	(2.5–10.0)	10	(8.8–12.5)	5	(0.0–10.0)	0.028
OCS maintenance, N (%)	17	(77)	8	(100)	9	(64)	0.115
Annualized exacerbation rate (# per year)	2	(1–3)	2	(2–3)	2	(1–3)	0.416
Serum eosinophil count (*10^9/L)	0.3	(0.1–0.5)	0.3	(0.0–0.5)	0.3	(0.1–0.5)	0.779
FEV1 pre-bronchodilator (%predicted)*	70	(58–78)	63	(48–73)	72	(63–82)	0.151
FeNO (ppb)*	53	(23–73)	43	(11–99)	55	(23–70)	0.941

The table describes patient characteristics at baseline and compares non-responders to responders

FeNO fractional exhaled nitric oxide, *FEV1* forced expiratory volume in 1 s, *OCS* oral corticosteroids

* Median (IQR)

Table 2 Asthma-related outcomes at baseline and 8 weeks

		Non-responder (N = 8)		Responder (N = 14)		*p* value
ACQ	Baseline	2.57	(2.09–3.33)	2.33	(1.17–2.50)	0.204
	8 Weeks	1.69	(1.25–2.25)	0.67	(0.50–1.50)	0.018
	Delta	− 1	(− 1.32 to − 0.40)	-0.66	(− 1.66 to − 0.37)	0.800
AQLQ	Baseline	5	(3.90–5.15)	5.21	(4.89–5.89)	0.168
	8 Weeks	5.16	(4.20–5.49)	6.39	(5.77–6.63)	0.009
	Delta	0.35	(0.28–0.45)	0.78	(0.10–1.22)	0.128
OCS dose (mg/day)	Baseline	10	(8.8–12.5)	5	(0.0–10.0)	0.028
	8 Weeks	6.3	(5.0–12.5)	2.5	(0.0–7.5)	0.081
	Delta	− 1.25	(− 5.0 to 0.0)	0	(− 2.5 to 0.0)	0.451
Serum eosinophil count (*10^9/L)	Baseline	0.3	(0.0–0.5)	0.3	(0.1–0.5)	0.779
	8 Weeks	0.0	(0.0–0.1)	0.0	(0.0–0.0)	0.017
	Delta	− 0.2	(− 0.5 to 0.0)	− 0.3	(− 0.6 to − 0.1)	0.596
FEV1 pre-bronchodilator (%pred)	Baseline	63	(48–72.5)	72	(63–82)	0.151
	8 Weeks	71	(44–91)	91	(67–97)	0.116
	Delta	3	(− 3 to 86)	10	(− 5 to 21)	0.590
FEV1 post-bronchodilator (%pred)	Baseline	66	(45–86)	81.5	(70.5–86.5)	0.204
	8 Weeks	76	(51–96)	93	(71–103)	0.160
	Delta	0	(− 4 to 3)	4	(2–14)	0.130
PEF (%pred)	Baseline	58	(47–92)	78	(61–89)	0.246
	8 Weeks	72	(49–95)	86	(76–95)	0.310
	Delta	3.5	(− 4 to 15)	6	(− 4 to 15)	0.968
FeNO (ppb)	Baseline	43	(11–99)	55	(23–70)	0.941
	8 Weeks	38	(17–72)	44	(28–55)	0.710
	Delta	− 9	(− 22 to 8)	2	(− 9 to 12)	0.297

The table describes asthma-related parameters at baseline, 8 weeks and the change in these parameters. All values are medians (IQR)

ACQ asthma control questionnaire, *AQLQ* asthma-related quality of life questionnaire, *FeNO* fractional exhaled nitric oxide, *FEV1* forced expiratory volume in 1 s, *OCS* oral corticosteroids, *PEF* peak expiratory flow

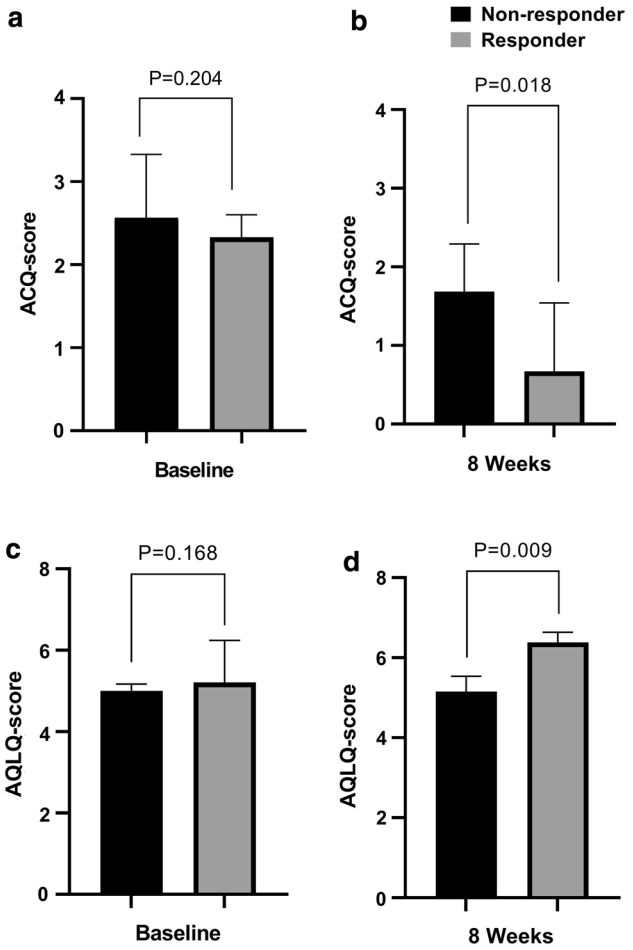

Fig. 1 Median and interquartile range of patient-reported outcome measures at baseline and 8 weeks for non-responders (black) and responders (grey). Panel **a** ACQ-score at baseline. Panel **b** ACQ-score at 8 weeks. Panel **c** AQLQ-score at baseline. Panel **d** AQLQ-score at 8 weeks. Abbreviations: ACQ: Asthma Control Questionnaire, AQLQ: Asthma-related Quality of Life Questionnaire

This occurred despite a statistically significant reduction of the daily OCS dose in the population. Furthermore, all patients with well-controlled asthma at 8 weeks were long-term responders. The results in this study suggest that incorporation of early changes in asthma-related parameters could help in the early detection of long-term responders to mepolizumab treatment.

A strength of this study is the real-world character, giving detailed information about the first period of mepolizumab treatment in a severe asthma centre. A limitation of the current study is the number of patients and the single-centre data, warranting caution when interpreting these results, and limiting the statistical power. Due to the small sample size, multivariable analysis, correcting for possible confounders, and exploration of the optimal ACQ cut-off using a ROC-curve were deemed unfeasible.

In the DREAM study, one of the mepolizumab phase II clinical trials, the first observed reduction in serum eosinophil counts occurred 4 weeks after the initial mepolizumab injection [8]. The early improvement in asthma control might be related to the fast eosinophil reduction. However, in the current study, no association between asthma control at 8 weeks and eosinophils was found. Recently, Numata et al. also explored predictors for mepolizumab response after 52 weeks in 24 Japanese patients. In this small study, multivariable analysis indicated that lower baseline BMI predicted response to mepolizumab treatment. This was not found in our study, and elucidating the influence of BMI on mepolizumab outcomes remains an objective for future studies. Numata et al. also found improvement after 3 months of treatment in eosinophil count, FeNO, and ACT-score, indicating the rapid onset of effects of mepolizumab treatment. In contrast to our study, differences at 3 months between responders and non-responders were not reported [9]. The summary of product characteristics of mepolizumab demands annual treatment evaluation, while the Global Initiative for Asthma (GINA) advises 16 weekly response evaluations, resulting in several evaluations before long-term treatment response is established [6]. The results in our study suggest that patients receiving mepolizumab therapy with an ACQ-score ≤ 0.75 at 8 weeks are unlikely to need this extensive monitoring, for they are very likely to be long-term responders. Objective clinical measurements, like spirometry data, did not improve after 8 weeks in our study, while we did observe a reduction of the OCS maintenance dose. Severe asthma is associated with airway remodeling and while the PROMs improve very rapidly, this rapid improvement can possibly not be expected in lung function [10]. Patients requiring higher OCS maintenance doses at baseline were less likely to be long-term responders. These patients might experience more severe asthma, decreasing their capability to be long-term responders. Therefore, the baseline OCS dose should be taken into account in the prediction of long-term response. However, while different at baseline, the OCS dose was not different at 8 weeks between non-responders and responders, as opposed to the PROMs. This may indicate that the OCS dose is less suitable to evaluate treatment response at 8 weeks. This advocates the use of PROMs in the therapy evaluation after initiating mepolizumab treatment. The decision at 8 weeks to identify patients that require less follow-up, leads to personalized follow-up, enabling pulmonologists to shift their focus to patients less likely to be long-term responders to mepolizumab therapy.

Future studies should include more patients from different centres to explore the consistency of the results in other populations, and to enable statistical stratification for baseline values. Furthermore, these studies should explore whether response after 52 weeks endures or decreases, to

what extent neutralizing antibodies develop and how this influences long-term response. The results in this study show a strong relationship between early improvement in PROMs and long-term therapy continuation. However, it might be more in the doctors' and patients' interest to identify non-responders at an early moment. Whether the addition of early changes in PROMs could help in the early identification of non-responders, remains an objective for future studies.

Conclusion

Expert groups and policy makers around the world attempt to achieve consensus about the evaluation of biological therapy in severe asthma and prediction of response on the long-term. In our study we found that early changes in ACQ and AQLQ may contribute to the prediction of mepolizumab response. This encourages further exploration of the applicability of early changes in PROMs in the clinical process. An early decision about personalized follow-up enables pulmonologists to allocate their valuable time to the patients that actually need close monitoring, improving the health-care process concerning biological treatment of severe asthma.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest Mr. Kroes reports grants from Astra Zeneca, outside the submitted work. Dr. Zielhuis reports grants from Astra Zeneca, personal fees from Novartis, personal fees from GSK, personal fees from Sanofi, personal fees from Lilly, personal fees from MSD, outside the submitted work. Dr. van der Meer has nothing to disclose. Dr. de Jong has nothing to disclose. Dr. Ten Brinke reports grants, personal fees and other from GSK, grants, personal fees and other from TEVA, grants, personal fees and other from AstraZeneca, other from Sanofi, other from Boehringer Ingelheim, outside the submitted work. Dr. Van Roon has nothing to disclose.

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