The perceived waning of biologics in severe asthma

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Original Research

The perceived waning of biologics in severe asthma☆

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ABSTRACT

Background: Biologics are highly effective in severe asthma and used at fixed dosing intervals. However, in clinical practice, dosing intervals are sometimes shortened if patients perceive a decreased biologic effect before the next administration. The occurrence and clinical relevance of this perceived waning of biological effect is unknown.

Objective: To explore (1) the frequency, severity and conditions, (2) associated symptoms and (3) relationship with clinical characteristics of the patient-perceived waning effect of biologics before the next administration.

Methods: Severe asthma patients receiving biological treatment ≥4 months were included. Based on 17 semi-structured patient interviews, we developed a questionnaire focusing on the waning effect of biologics before the next administration, which was distributed among 129 patients. Clinical characteristics, including asthma control (ACQ) and quality of life (AQLQ) scores, were collected from patient files.

Results: 65/101 patients who completed the questionnaire reported a waning of biological effect, graded as severe (median (IQR) 6.5 (5–7.5) on a 0–10 BORG-scale). Waning manifested in a broad spectrum of symptoms. Patients reporting waning had higher ACQ and lower AQLQ scores versus those without ($p < 0.05$) and higher BORG-scores were associated with higher exacerbation rate ($\rho = 0.309$, $p = 0.013$). A third of all patients were in favor of extending or shortening their dosing interval.

Conclusion: Two-thirds of severe asthma patients report waning of biologic effect at the end of the dosing interval, which is associated with poorer asthma control and quality of life. The diversity in observed waning of effect opens the way for research into more individualized dosing of biologics.

1. Introduction

The recent approval of biologics to treat patients with severe asthma has led to major changes in severe asthma care. These biologics target type 2 inflammatory pathways and have been shown to markedly reduce asthma exacerbations and oral corticosteroid (OCS) use, as well as improve asthma symptoms, lung function and quality of life [1–6]. However, there is considerable heterogeneity in clinical response to biologics and not all patients respond equally well [7]. Treatment is therefore evaluated after 4–6 months and discontinued or switched to another biologic if the response is deemed insufficient [8].

Within responders, there are also degrees of response. Some patients demonstrate a super-response to the biologics, while other patients have only a partial response with residual disease manifestations [7,9]. In clinical practice, this sometimes leads to adjustment of the dosing intervals, despite the fact that the summaries of product characteristics state that the biologics need to be prescribed in fixed dosing intervals. For example, there are patients with an excellent response in whom prolongation of the dosing interval is possible without loss of asthma control [10]. On the other hand, some patients feel that their asthma symptoms worsen towards the end of their dosing interval, sometimes leading to dose escalation by shorter dosing intervals [11]. Several registration studies assessed the dosing interval responsiveness and found that biological efficacy was sustained over the course of the

☆ All participants signed informed consent before participating to this study. A medical ethics committee waived the necessity to comply with the Medical Research Involving Human Subjects Act.

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dosing interval, but these are subject to the controlled environment of randomized controlled trials (RCTs) and mainly focused on objective outcome measures [12–14].

These signals from clinical practice suggest that individualized dosing of biologics may be possible and desired for a subset of patients. Such a personalized approach, in which the maintenance of asthma control and health-care costs are essential, could contribute to an optimal application of the costly biologics. However, guidelines or objective parameters for dose adjustments are lacking and adjustment of dosing intervals, if any, is performed empirically based on the subjective experiences of patients. Currently, data on these patients experiences are lacking. We have no insight into the frequency and severity of the perceived waning of biological effect at the end of the dosing interval, nor do we know what characterizes this perception and whether it is clinically relevant.

Therefore, the aim of this study is to explore in patients with severe asthma (1) the frequency, severity and conditions of the patient-observed waning effect of biologics prior to the next administration. In addition, we evaluated the (2) characteristics and (3) association with asthma-related outcomes of this perceived waning biological effect.

2. Methods

2.1. Study design and patients

This was a cross-sectional, observational study performed in the severe asthma centre of the Medical Centre Leeuwarden, the Netherlands. The study population consisted of all adult patients receiving biological treatment (omalizumab, mepolizumab, reslizumab, benralizumab or dupilumab) for severe asthma $\geq$4 months. All patients were diagnosed with severe asthma before initiating biological treatment based on the ERS/ATS guidelines [15]. Inhaled medication doses, inhaler technique and adherence were optimized before and during biological treatment, in concordance with the Dutch Severe Asthma Guidelines [16].

The study included two phases. In the first phase, a sample of 20 patients from the total study population was selected, taking into account differences in sex, age and type of biologic (Supplementary Table S1), in which semi-structured interviews were conducted for the purpose of developing a structured questionnaire. In the second phase of the study, the developed questionnaire was distributed over the rest of the study population in order to quantify the items that were derived from the interviews.

2.2. Data collection

2.2.1. Interviews

An interview guide was developed with input from a pulmonary physician, a specialized pulmonary nurse and knowledge from a previous study [17]. Qualitative semi-structured interviews then were conducted to gather information from patients to explore what, in the patients' own words, are their experiences with biological treatment for severe asthma, whether these patients perceive a waning of the biological effect at the end of the dosing interval, and what symptoms are associated with this phenomenon.

Conducting the interviews was an iterative process, where new topics and answers from previous interviews were introduced to upcoming interviews [18]. New topics were introduced during the first few interviews and could be discussed during later interviews. All interviews were conducted by two researchers (JAK and LVH), recorded using ZOOM software and transcribed, coded and analysed using ATLAS. ti, version 22.

2.2.2. Questionnaire

Based on the results from the interviews, a questionnaire was developed in order to quantify the findings from the interviews in the rest of the population. This questionnaire was tested for comprehensibility and legibility by approaching two patients that were not part of the interviewed sample. Any feedback was incorporated in the final version of the questionnaire (Supplementary file 1). This questionnaire was distributed over the remaining non-interviewed severe asthma patients by post. After 3 weeks, patients were reminded by telephone if no reaction was received. After another 3 weeks, data collection was halted and data analysis commenced.

2.2.3. Measurements

In addition to the questionnaire, study characteristics were collected from the nearest (max. 3 months before/after taking the questionnaire) standard evaluation moment in the patients' files. These included: patient demographics, asthma characteristics, medication (biologic dose, biologic dosing interval, OCS use, OCS maintenance dose, previous biologic), number of exacerbations in the last 12 months, lung function measurements (FEV_1), inflammatory markers (peripheral blood eosinophils, fractional exhaled nitric oxide (FeNO)), and comorbidities (nasal polyposis, chronic rhinosinusitis, bronchiectasis). Inhalation therapy was optimized before and during the treatment.

2.3. Statistical analysis

Continuous variables were expressed as means (SD) or medians (IQR) when applicable and categorical variables as percentages. Differences between the interviewed group and the questionnaire group were analysed using t-tests and Mann-Whitney U-tests or Chi [2]-tests when applicable. The outcomes from the questionnaire were analysed using descriptive statistics. The association of waning of the biological effect and patient characteristics was analysed using t-tests and Mann-Whitney U-tests. The association between the BORG-scale (ranging from 0 (no need) to 10 (extreme need for the next administration)) was analysed using the Spearman Rank Correlation. A *P*-value $<$0.05 indicated statistical significance. All statistical analyses were performed with IBM SPSS Statistics version 26.0.

3. Results

3.1. Patients and development of the questionnaire

We identified 146 patients receiving biological treatment for severe asthma for at least 4 months. Of the 20 patients selected for the interviews, 17 patients agreed to be interviewed. Table 1 shows several themes and quotes that were found in the interviews. Based on these findings, the questionnaire in Supplementary File 1 was drafted.

This questionnaire was distributed to the remaining 129 patients and completed by 101 of them (78.3%) (Fig. 1). Table 2 summarizes the characteristics of the patients responding to the questionnaire. Fifty-seven percent of the 101 participants were male, 63% of patients had adult-onset asthma. Median (IQR) duration of biological treatment was 33.1 (17.8–46.0) months and during this use of biologics, the majority of the patients had a controlled disease with no asthma exacerbations in the previous year. As compared to the interviewed patients, the patients responding to the questionnaire were more often former smokers with lower levels of FEV_1 (Supplementary Table S2).

3.2. Frequency, severity and conditions of waning of biological effect

Sixty-five patients (64.4%) gave a positive answer to the question "Do you notice that the effect of the biologic wears off before you take/receive the next injection/infusion?" (Fig. 2a). On a BORG-scale ranging from 0 (no need) to 10 (extreme need for the next administration) these 65 patients rated the severity of the need for a next administration with a score of 6.5 (5.0–7.5) (median (IQR)) (Fig. 2b). Nearly half (47.7%) of patients experienced this effect with every administration, and 12 (18.4%) in specific seasons (Fig. 2c).

Table 1
Findings from patient-interviews, themes (in bold) and quotes (in italics).

Patients were generally very satisfied with their biological treatment.
"It was a one-hit. I have not been sick [since initiating biological treatment], I feel super, I can do all sorts of things and I have no symptoms whatsoever. Sometime I think: I do not have asthma anymore."
Several patients mentioned that the final week(s) of the dosing interval is associated with asthma symptoms in different gradations and conditions, while some patients reported the opposite.
"That last week is a drama. I am demolished [that last week] and something has to be done. I either end up in the hospital or nebulize more. And then you do nothing on a day, you undertake nothing. Socially, you do not have anything. That is difficult."
"I do not feel that I need the [biological] medication. I do take the medication because I know what happens if I don't, but I do not feel anything else towards the end of the interval."
When asked what symptoms contribute to the perceived waning, a variety of symptoms was mentioned.
"I feel less energy and less stamina, more tired, towards the end of the dosing interval."
"It usually starts with shortness of breath and if that develops, I start coughing."
Patients reported several solutions when symptoms occurred.
"I nebulize more when I feel symptoms."
"I then need [towards the end of the dosing interval] to take my Foster more often, I then go to 3x2 instead of 2x2 daily."
Finally, several patients expressed the wish for an adjusted dosing interval, either prolonging due to good asthma control or shortening due to waning of the biological effect.
"I do not require the administration sooner. A week later might be possible. If my doctor would like to experiment with an administration every 9 weeks, I would be open to that."
"If I could take the gift on the, let's say, tenth or eleventh day [of a two-week interval], that would be better for me."

Fig. 1. Flow chart.
Legend to Fig. 1: Flow chart of selected patients.

3.3. Symptoms experienced with waning of biological effect

Patients were asked: "What symptoms do you experience in the period of waning of effect?". A wide variety of symptoms was reported, with reduced stamina, shortness of breath and fatigue being the most common (Fig. 3). Patients reported that symptoms improved within 2 (2–4) days (median; IQR) after the next biologic administration.

3.4. Waning and asthma-related characteristics

Characteristics of the patients with or without a perceived waning of effect are compared in Table 2. Patients experiencing waning of the biological effect used biological treatment shorter compared to those not experiencing waning and a trend towards a difference between biologics is observed. The annual exacerbation rate and maintenance OCS use did not differ between both subgroups. However, patients perceiving waning of effect had higher ACQ-scores and lower AQLQ-scores than those without a need for early administration (Fig. 4).

Within the 65 patients who perceived waning of biological effect, a higher BORG-score for severity of waning was associated with lower AQLQ scores ($\rho = -0.292$, $p = 0.031$) and a higher rate of exacerbations ($\rho = 0.309$, $p = 0.013$), but no significant association was observed with ACQ and FEV_1.

3.5. Coping and preferences

When asked what actions are being taken by the patients when perceiving the waning of effect, 42 patients (64.6%) state that they slow down and undertake fewer activities and 36 patients (55.4%) indicate that they increase the frequency of their inhaled controller medication.

Finally, when focusing on the wishes regarding dosing interval adjustment, 35 (34.6%) of the total population indicated that they were in favor of such an adjustment, either extending or shortening the interval: Twenty-eight of 65 patients with perceived waning of biologic effect indicate that they wish to shorten their dosing interval. The median (IQR) number of days they would like to receive the injection/infusion earlier is 4 (3–5), 7 (6–7) and 7 (7–14) for biologics dosed at 2, 4 and 8 weekly intervals, respectively. Seven of 36 patients with no observed waning effect indicate that they would be willing to extend their dosing interval if suggested by their physician.

4. Discussion

This study, using a newly developed questionnaire, found that two-thirds of patients with severe asthma report a waning of biological effect at the end of the dosing interval, the majority of whom report this as severe. Patient-reported waning manifested in a wide variety of symptoms, with reduced stamina, shortness of breath and fatigue being the most common. Compared to those without, patients with perceived waning had poorer asthma control and quality of life, and higher exacerbation rates with increasing severity of perceived waning. Several of these patients indicated a wish to shorten their dosing interval, whereas, on the other hand, a subset of the patients with no perceived waning effect were willing to increase their dosing interval. These findings encourage further research into the effectiveness and costs of a more personalized dosing of biologics for severe asthma.

This is the first study investigating the perceived waning of biological effect in a large severe asthma population in which the patients received biological treatment for a long period of time and the majority of the patients achieved controlled asthma. While several RCTs found that the efficacy of biological treatment was consistent during the course of the dose interval, little is known about the patient-observed decreasing effect of their biological treatment over the course of the dosing interval [12–14]. This phenomenon was recently mentioned in an international study involving focus-groups and underpinned the interval adjustment in a case report [11,19]. In addition, in a small proof-of-principle study it was shown that patient-reported need for the next omalizumab administration was associated with lower serum levels of omalizumab. The suggestion was made that combining patient-reported signals and objective biologic trough levels could provide healthcare professionals with the tools to successfully personalize biological treatment [17]. Our study, which quantifies and qualifies our patients' signs of a declining effect, can be seen as a first step in such an approach.

A strength of this study is that interviews were conducted in a broad representation of the patient population to ensure that all topics brought up by patients were covered in the questionnaire. Furthermore, not only was the willingness to participate in the interviews good, but especially the response rate of 78.3% to the questionnaire was very high. In addition to the questionnaire, patient- and asthma characteristics were systematically collected in clinical practice and therefore well-described, further contributing to the quality of this study. Our study has some limitations as well. First, this was a single-centre study, which may limit the generalizability of our results to other patient populations. Second, there is no validated questionnaire to assess the perceived

Table 2
Baseline characteristics for the total population, and stratified for patients with and without perceived waning of biological effect.

Patient characteristic		All patients (N = 101)	With waning of effect (N = 65)	Without waning of effect (N = 36)	*P*-value
Age[a] **(y)**		60.0 (53.0–67.0)	60.0 (52.0–67.0)	60.0 (54.5–67.0)	0.94
Male gender, N (%)		58 (57.4)	40 (61.5)	18 (50.0)	0.26
BMI[a] **(kg/m^2)**		26.1 (23.6–30.2)	26.3 (24.1–30.5)	25.8 (23.5–28.6)	0.31
Former smoker, N (%)		46 (45.5)	30 (46.2)	16 (44.4)	0.82
Pack years[a]		8.0 (3.0–15.0)	9.0 (5.0–14.7)	5.5 (2.0–16.0)	0.35
Late asthma onset, N (%)		64 (63.4)	41 (63.1)	23 (63.9)	0.94
Age of asthma onset[a] **(y)**		47.0 (27.0–55.0)	50.0 (30.0–55.0)	43.0 (20.0–54.0)	0.23
Atopy, N (%)		47 (46.5)	28 (43.1)	19 (52.8)	0.39
Exacerbations last year[a]		0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.73
Prescribed daily OCS dose[a] **(mg/day)**		0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.82
Previous biologic, N (%)		35 (34.7)	19 (29.2)	16 (44.4)	0.12
ACQ score[a]		1.00 (0.50–1.83)	1.17 (0.67–2.00)	0.75 (0.33–1.42)	**0.015**
AQLQ score[a]		6.08 (5.27–6.59)	5.69 (4.98–6.52)	6.44 (5.93–6.70)	**0.005**
FEV$_1$ pre (%pred)[a]		83.0 (70.0–95.0)	82.0 (70.0–91.0)	87.0 (70.0–98.0)	0.35
FeNO (ppb)[a]		26.0 (16.0–46.0)	27.0 (18.0–43.0)	24.0 (15.0–59.0)	0.84
Serum eosinophils (10 [9]/L)[a]		0.02 (0.00–0.10)	0.01 (0.00–0.07)	0.08 (0.00–0.30)	0.11
Bronchiectasis, N (%)		21 (20.8)	12 (18.5)	9 (25.0)	0.44
CRSwNP, N (%)		39 (38.6)	25 (38.5)	14 (38.9)	
Biologic, N (%)	Omalizumab	13 (12.9)	6 (9.2)	7 (19.4)	0.088
	Mepolizumab	19 (18.8)	9 (13.8)	10 (27.8)	
	Reslizumab	5 (5.0)	4 (6.2)	1 (2.8)	
	Benralizumab	47 (46.5)	36 (55.4)	11 (30.6)	
	Dupilumab	17 (16.8)	10 (15.4)	7 (19.4)	
Dosing interval, N (%)[b]	2 weekly	17 (19.1)	10 (17.5)	7 (21.0)	0.180
	4 weekly	30 (33.7)	16 (28.1)	14 (43.8)	
	8 weekly	42 (47.2)	31 (54.4)	11 (34.4)	
Treatment duration (months)[a]		33.1 (17.8–46.0)	29.5 (17.3–41.5)	40.0 (25.4–64.2)	**0.039**

Abbreviations: ACQ: Asthma control questionnaire, AQLQ: Asthma-related quality of life questionnaire, BMI: Body mass index, CRSwNP: Chronic rhinositis with nasal polyps, FeNO: Fractional exhaled Nitric Oxide, FEV$_1$: Forced exhaled volume in 1 s, OCS: Oral corticosteroids.
[a] Median, IQR.
[b] Percentages calculated over patients with 2, 4 or 8 weekly dosing intervals.

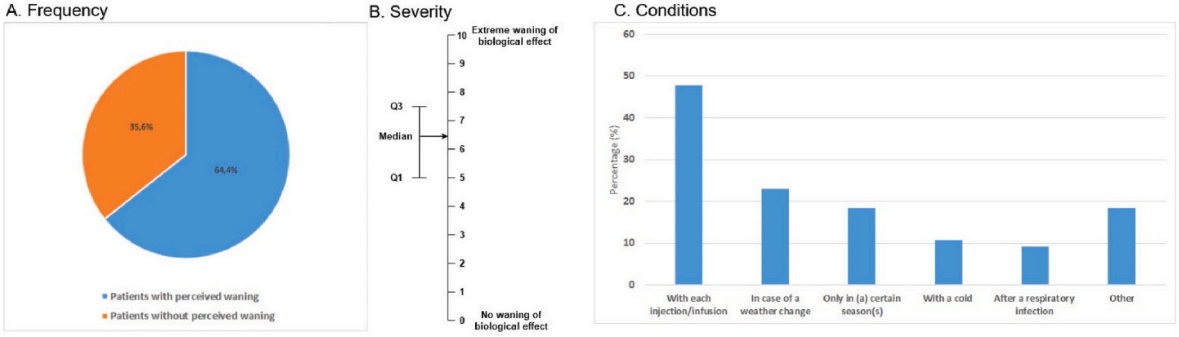

Fig. 2. Frequency, severity and conditions of perceived waning of biological effect.
Legend to Fig. 2: These figures show the frequency (panel a, N = 101), severity (panel b, N = 65) and conditions (panel c, N = 65) of perceived waning of biological effect in patients with severe asthma.

waning of biological effect and although we have tried to cover all aspects in our newly-made questionnaire, we cannot rule out that using a different questionnaire would have yielded different results. Both the interviews and the questionnaire were self-reported, which might have introduced bias. This is however inherent to our methodology. The formulation of some questions was dichotomous (for example question 11) in order to guide the patient through the questionnaire. A 5-point scale might have introduced more nuance in these cases. Nevertheless, we believe that the findings of our exploratory study give a clear signal which provides an important objective for future research. Furthermore, patients experiencing a waning of biological effect might be more interested in completing the questionnaire, possibly leading to a selection bias. Though patients who did not respond to the questionnaire were generally younger and had more often early-onset atopic asthma (data not shown), we do not expect this to have a major impact on our results, especially given the high response rate, although we cannot rule this out completely. Finally, a drawback of our study is the lack of more objective outcomes to explain our findings, for example assays to determine biological serum levels. However, our findings will hopefully convince multiple parties to investigate the effectiveness and costs of a more personalized dosing of biologics for severe asthma, using patients' perceptions and objective measures such as biological serum levels.

How can the patient-observed waning of biological effect and the difference between patients in this regard be explained? First, pharmacokinetic variabilities may be considered. Here we may learn from diseases such as inflammatory bowel disease and rheumatoid arthritis where biologics have been used for a long time. For example, in rheumatoid arthritis, due to inter-patient variability in clearance, infliximab trough levels varied and low through levels were associated with decreased disease control approaching the end of the dosing interval [20]. Thus, inadequate serum levels and enhanced clearance of the biologics could explain the findings in our study. In addition, biologic administration may lead to an endogenous antibody response, which may alter the pharmacokinetics and efficacy of the biologics [21]. A

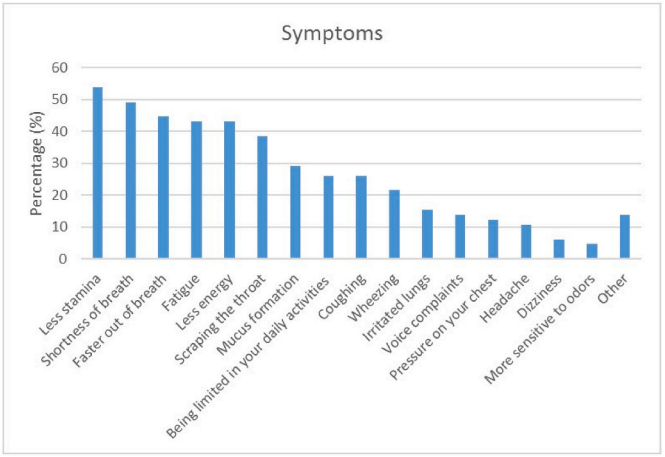

Fig. 3. Symptoms experienced with waning of biological effect
Legend to Fig. 3: This figure shows the reported symptoms when patients (N = 65) experience waning of biological effect.

recent meta-analysis reported that approximately 2.9% of individuals in the included studies developed anti-drug antibodies [22]. However, the clinical implication of anti-drug antibody formation is not yet fully explored for the biologics used in severe asthma, but might become relevant in the near future. As there is a large difference between the prevalence of waning in our study and the low reported prevalence of anti-drug-antibodies, this phenomenon might not completely explain our findings. Third, we also cannot exclude the possibility of coincidence or a nocebo effect explaining our findings [23]. For example, it has been studied that patients with asthma can develop or resolve bronchospasm based on suggestion [24]. However, the association found between the perceived waning effect and poorer scores of the validated and commonly used questionnaires ACQ and AQLQ could also indicate a subgroup with more uncontrolled disease in which there is undertreatment, and which could benefit from dose escalation by shortening of dosing intervals. Finally, on the other side of the palette we see patients who do not experience any decrease in biological effect and opt for extending the dosing interval, which may be a manifestation of their super-response or even asthma remission [25]. Patients with waning seem to be treated for a shorter period than patients without waning, though the treatment period in both subgroups is long (29.5 *vs.* 40 months respectively). This observation might be driven by a subgroup of patients that receive biologics for a shorter period of time and experience waning because the effect of the biologic is not yet fully achieved and requires more time. We tried to overcome this aspect by only including patients that receive biologics longer than 4 months, but this inclusion criterion might still not be optimal. Furthermore, there seems to be a difference between incidence in waning between the biologics, though our methodology was not designed to study this difference. This observation might be related to a difference in efficacy, dosing interval, subjective aspects or is merely a coincidence. Due to the small numbers in our study, this observation warrants further research in larger populations.

Our results have several implications. The majority of the patients reported a waning of biological effect. Whether this is due to undertreatment with biologics and might improve with dose escalation is currently unknown. Therefore, future studies confirming our findings in a wider population and elucidating the mechanism behind this phenomenon are warranted. In other inflammatory diseases, such studies included dose escalation or de-escalation trials and led to development of therapeutic drug monitoring (TDM), which provides objective tools to improve biological treatment [26–30]. Such objective tools could be a welcome addition to severe asthma clinical care, because they could help optimize treatment with the costly biologics and improve patient satisfaction. In addition, longitudinal studies exploring the waning effect over the course of the dosing interval, supplemented with other parameters like validated questionnaires (ACQ, AQLQ) and pulmonary function would further elucidate the findings from our study. Consequently, studies on the clinical added value and cost-effectiveness of adjusting dosing intervals based on objective parameters and patient-perception are warranted, pursuing shared decision-making and personalized medicine.

In conclusion, this explorative study finds that two-thirds of severe asthma patients report a waning of biological effect at the end of the dosing interval, which results in a wide variety of symptoms and is associated with poorer asthma control and quality of life. The diversity in perceived waning of biological effect opens the way for research into more individualized dosing of biologics in severe asthma.

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CRediT authorship contribution statement

J.A. Kroes: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, and, Writing – review & editing. **L.H.G. Van Hal:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft. **L. Van Dijk:** Conceptualization, Methodology, Supervision, Writing – original draft, and, Writing – review & editing. **S.W. Zielhuis:** Conceptualization, Methodology, Supervision, Writing – original draft, and, Writing – review & editing. **A.N. Van Der Meer:** Conceptualization, Data curation, Methodology, Supervision, Writing – original draft, and, Writing – review & editing. **E.N. Van Roon:** Conceptualization, Methodology, Supervision, Writing – original draft, and, Writing – review & editing. **A. Ten Brinke:** Conceptualization, Data curation, Methodology, Supervision, Writing – original draft, and, Writing – review & editing.

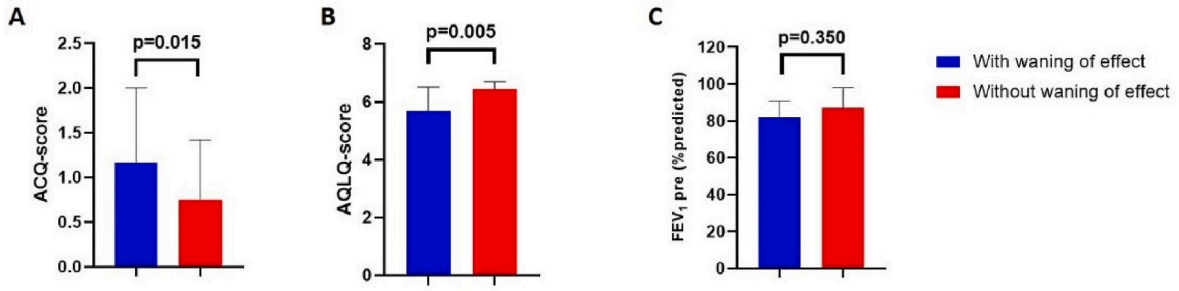

Fig. 4. Perceived waning of biologic effect and asthma control, quality of life and lung function.
Legend to Fig. 4: This figure shows asthma-related outcomes for patients with and without perceived waning of biological effect. Abbreviations: ACQ: Asthma Control Questionnaire, AQLQ: Asthma-related Quality of Life Questionnaire.

Declaration of competing interest

There is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2023.107416.

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