Criteria for evaluation of response to biologics in severe asthma – the Biologics Asthma Response Score (BARS)

Kriterien zur Evaluation des Ansprechens auf Biologika bei schwerem Asthma – der Biologics Asthma Response Score (BARS)

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ABSTRACT

Background The introduction of monoclonal antibodies (biologics) has revolutionized the therapy of severe asthma. Even though there is a response in the majority of patients, the degree of response varies. To date criteria for assessment of response to biologics are not consistently defined.

Aim To define criteria for evaluation of response to biologics that are precise, simple and suitable for daily use in order to guide decision-making regarding continuation, switching or stopping of biological therapy.

Methods 8 physicians with large experience in this indication, supported by a data-scientist, developed a consensus on criteria to evaluate response to biologics in patients with severe asthma.

Result We developed a combined score based on current literature, own experience and practicability. It uses the main criteria exacerbations, oral corticosteroid (OCS) therapy and asthma control (asthma control test, ACT). We defined thresholds for "good response", "response" and "insufficient response" rated with a score of "2", "1" and "0" respectively: annual exacerbations ("0 or reduction ≥ 75 %", "reduction 50–74 %", "reductio < 50 %"), daily OCS dose ("stopping or reduction ≥ 75 %", "reduction 50–74 %", "reduction < 50 %"), asthma control ("ACT increase ≥ 6 or ≥ 3 with result ≥ 20", "ACT increase 3–5 with result < 20", "ACT increase < 3"). Additional individual criteria like lung function and comorbidities may be important for evaluation of response. We propose 3, 6 and 12 months timepoint for assessment of tolerability and response. Using the combined score, we developed a scheme to guide the decision whether switching the biologic should be considered.

Conclusion The Biologic Asthma Response Score (BARS) serves as objective and simple tool to evaluate response to biologic therapy using the three main criteria exacerbations,

OCS use and asthma control. A validation of the score was initiated.

ZUSAMMENFASSUNG

Hintergrund Die Einführung monoklonaler Antikörper (Biologika) hat die Therapie des schweren Asthmas revolutioniert. Auch wenn die Mehrheit der Patienten ein Ansprechen zeigt, kann dieses unterschiedlich ausgeprägt sein. Bislang sind Kriterien zur Beurteilung des Ansprechens auf Biologika nicht einheitlich definiert.

Ziel Definition von konkreten, einfachen und praxistauglichen Kriterien zur Bewertung des Ansprechens auf Biologika bei Patienten mit schwerem Asthma, um eine Entscheidungshilfe bzgl. Fortführung, Umstellung oder Beendigung der Therapie zu geben.

Methoden 8 Ärztinnen und Ärzte mit umfangreicher Erfahrung in dieser Indikation, unterstützt durch einen Data Scientist, erarbeiteten einen Experten-Konsens hinsichtlich Kriterien zur Evaluation des Ansprechens auf Biologika-Therapien bei Patienten mit schwerem Asthma.

Ergebnis Auf Basis aktueller Literatur, eigener Erfahrungen und Praktikabilität wurde ein kombinierter Score entwickelt. Dieser berücksichtigt als Hauptkriterien Exazerbationen, Dauertherapie mit oralen Steroiden (OCS) und Asthmakontrolle (Asthma Control Test, ACT). Schwellenwerte für die Einschätzung „gutes Ansprechen“, „Ansprechen“ und „unzureichendes Ansprechen“ wurden definiert und mit „2“, „1“ bzw. „0“ Punkten bewertet: jährliche Exazerbationen („0 oder Reduktion ≥75 %“, „Reduktion 50–74 %“, „Reduktion <50 %“), Tagesdosis OCS („Absetzen oder Reduktion ≥75 %“, „Reduktion 50–74 %“, „Reduktion <50 %“), Asthmakontrolle („ACT Anstieg ≥6 oder ≥3 mit Endwert ≥20“, „ACT Anstieg 3–5 mit Endwert <20“, „ACT Anstieg <3“). Zusätzliche individuelle Kriterien,wie Lungenfunktion und Komorbiditäten, können für die Bewertung des Therapieansprechens wichtig sein. Verträglichkeit und Ansprechen sollten nach 3, 6 und 12 Monaten erfasst werden. Anhand des Scores wurde ein praxisnahes Schema für die Entscheidung erarbeitet, ob ein Wechsel des Biologikums erwogen werden sollte.

Schlussfolgerung Der Biologics Asthma Response Score dient zur objektiven und einfachen Einschätzung des Ansprechens auf Therapie mit Biologikum auf Grundlage einer strukturierten Bewertung der drei Hauptkriterien Exazerbationen, oraler Steroidverbrauch und Asthmakontrolle. Eine Validierung des Scores wurde initiiert.

Introduction

In Europe, approximately 3–4 % of adults with asthma suffer from severe asthma (see box for definition) [1, 2]. In Germany, according to prescription data, 54,000 patients with asthma treated at stage 4–5 are uncontrolled [3]. A proportion of patients with severe asthma do not achieve adequate control of the disease despite optimised high-dose inhaled therapy. Biologics are the preferred choice over oral corticosteroids (OCS) after all other therapeutic measures have been exhausted, especially in patients who often require oral corticosteroids intermittently or permanently due to exacerbations [1, 2]. The currently approved biologics are listed in ▶ **Tab. 1**, [4–9]. The majority of patients benefit from treatment with a biologic, although the response may vary from individual to individual. There are many reasons for these differences in response.

For example, there may be several inflammatory drivers that are not all sufficiently covered by selective blocking of only one target protein. Also, a reliable prediction to which biologic a patient will best respond is not yet possible because of the lack of direct comparative studies and the overlapping of available biomarkers to phenotype and predict the response for the different antibodies. In addition, biomarkers show fluctuations over time, which can make classification difficult. Also, comorbidities (with or without type 2 inflammation) may be important.

Back in 2017, Buhl et al. developed a traffic-light system that distinguished super, intermediate and non-responders [10]. With the increasing number of approved biologics (currently six), the assessment of the response is becoming increasingly important. The aim is to provide the best possible treatment for the patient. However, there is still no uniform definition of parameters and timelines for classifying patients into these response groups.

A particular challenge in practice is the largest group of patients in terms of numbers, referred to in the traffic-light system as “intermediate responders”. For them, the question is what criteria and what time should be used as the basis to assess whether the success of the therapy is considered sufficient and whether the biologic that has been started should be continued, stopped or switched.

In the literature of recent years, there are various proposals for parameters and thresholds based on which the response has been assessed. Each was used to investigate specific issues (e. g., response to IL5 antibodies under practical conditions). The parameters used include exacerbations, use of OCS, symptom load (measured by the Asthma Control Test [ACT] or Asthma Control Questionnaire [ACQ]), lung function (measured by one-second capacity [FEV_1]), fractional exhaled nitric oxide (FeNO), eosinophil count, physicians’ global assessment, and the subjective assessment of the patients. All proposals are based on combinations of these parameters, but they are composed differently and use different thresholds. Some suggestions only distinguish between response and non-response to therapy, while others also define a partial response and others define a super response (▶ **Tab. 2**), [10–19]. Recently, a group of Spanish experts published an initial proposal for a score specifically designed to evaluate the therapeutic response to biologics. This is based on the parameters of FEV_1 (Forced expiratory volume in 1 sec), reduction of severe exacerbations, reduction of OCS, and symptom load, each with weighted thresholds [20, 21].

▶ **Tab. 1** Overview of approved biologics in the indication of severe asthma and associated phase 3 approval studies [4–8], table modified by [42].

Biologic	Target protein	Indication of asthma phenotype	Administration	Efficacy in phase 3 asthma studies: Improvement compared to placebo (different study populations do not allow for a direct comparison between the preparations)				
				Annualized Exacerbation rate	FEV_1	ACQ symptoms	OCS reduction (in the dedicated phase 3 study)	Approval for other diseases
Omalizumab	IgE	"Severe allergic asthma with sensitisation to a perennial allergen"	Every 2–4 weeks. s. c.	Reduction approx. 25–50 %	Slight improvement	Slight improvement	Not investigated	CSU, CRSwNP
Mepolizumab	IL-5	"Severe eosinophilic asthma"	Every 4 weeks. s. c.	Reduction approx. 50 %	Improvement approx. 100 ml	Slight improvement −0.44	50 % median	CRSwNP, HES, EGPA
Reslizumab	IL-5	"Severe eosinophilic asthma"	Every 4 weeks i. v.	Reduction approx. 50–60 %	Improvement approx. 110 ml	Slight improvement −0.25	Not investigated	–
Benralizumab	IL5 receptor α	"Severe eosinophilic asthma"	3 x every 4 weeks, then every 8 weeks s. c.	Reduction approx. 25–60 %	Improvement approx. 100–160 ml	Slight improvement −0.29	50 % median	–
Dupilumab	IL4 receptor α	"Severe asthma with type 2 inflammation"	Every 2 weeks s. c.	Reduction approx. 50–70 %	Improvement approx. 130–140 ml	Slight improvement −0.3	50 % median	AD, CRSwNP
Tezepelumab	TSLP	"Severe asthma"	Every 4 weeks s. c.	Reduction approx. 50–70 %	Improvement approx. 130 ml	Slight improvement −0.33	Not significant (to be re-examined with modified study design)	–

ACQ – Asthma Control Questionnaire; Ig – Immunoglobulin; IL – Interleukin; i. v. = intravenous; OCS – oral corticosteroids; s. c. – subcutaneous; TSLP – Thymic Stromal Lymphopoietin; AD – Atopic Dermatitis; CRSwNP – Chron. Rhinosinusitis with Nasal Polyps; HES – hypereosinophilic syndrome; EGPA – eosinophilic granulomatosis with polyangiitis.

The authors of this publication have extensive experience in the treatment of patients with severe asthma. A survey of participants at the beginning of the study revealed that there was no uniform approach to assess the response to therapy. Subjective judgement has so far played an important role in deciding whether to continue or switch therapy, based on experience in treatment with biologics and knowledge of the individual patient's history.

Therefore, in two face-to-face work meetings and a subsequent written vote, the authors developed the expert consensus presented here. It provides specific, uniform, simple, and practical criteria for objectively assessing the response to biologics at specific times, as well as guidance for deciding whether to switch to another biologic. This scheme is intended, on the one hand, to provide guidance to physicians with less experience in the treatment of severe asthma with biologics, and, on the other hand, to promote standardization of response assessement. However, the individual assessment of each patient by the treating physician remains essential.

SEVERE ASTHMA

Severe asthma, as defined by the National Care Guidelines (NVL), is present when at least one of the following applies, or would apply if therapy was reduced when treated with inhaled corticosteroids (ICS) at the maximum dose and at least with an additional long-term medication or oral corticosteroids (OCS) for more than 6 months/year:

- Respiratory obstruction: One-second capacity (FEV_1) < 80 % (FEV_1/FVC < LLN)
- Frequent exacerbations: ≥ two exacerbations requiring corticosteroids in the last 12 months
- Severe exacerbations: ≥ one severe exacerbation with inpatient treatment or ventilation in the last 12 months
- Partially controlled or uncontrolled asthma [NVL].

Methods and Results

Procedures for developing the expert consensus

1. Prioritising relevant parameters for responding to biologic therapy based on literature, personal experience, and practicality
2. Discussing and agreeing on specific thresholds for each parameter as well as timelines to assess whether there is a good response, a response, or an insufficient response
3. Developing and discussing ideas for a parameter-based score for the structured evaluation of the therapeutic response to biologics (e. g., total score, mean, visual); agreeing on the use of the mean
4. Clinical plausibility testing of the new score based on selected patient cases from the expert group
5. The next step is to validate the proposed score.

Setting the evaluation criteria

In a survey conducted prior to the first meeting, the eight participants were asked to identify the four most important parameters for assessing the response to therapy. By far the most frequently mentioned were:

1. Reduction of exacerbations (six mentions)
2. Reduction of OCS (seven mentions) and
3. Improving asthma control (seven mentions)

The improvement in quality of life and tolerability were mentioned four times, and the improvement in lung function was mentioned once.

In the face-to-face meeting, the asthma experts confirmed the three parameters reduction of exacerbations, reduction of OCS, and improvement of asthma control as the main criteria for assessing the response to therapy. It was agreed that additional criteria such as lung function, comorbidities, physical capacity, and patient satisfaction are complementary criteria to be taken into account.

While thresholds have been developed for the main criteria, which define (a) a good response, (b) a response, and (c) an insufficient response, the assessment of the complementary criteria takes place on an individual basis.

First main criterion: Reduction of exacerbations

According to the National Healthcare Guidelines (NVL) for Asthma, exacerbations are defined as "phases of a progressive increase in asthma symptoms and/or reduction in lung function [...], which go beyond the usual level of variability for the patient and require a change or intensification of therapy over several days" [2].

The reduction of exacerbations is of paramount clinical relevance in order to improve the prognosis and course of the disease. In addition to severe exacerbations (need for inpatient treatment, if necessary, ventilation), this also applies to moderate exacerbations (OCS required). However, there are no scientific studies that have established the minimally clinically important difference (MCID) for the reduction of exacerbations. Rather, there are various proposals in the literature for thresholds for reducing the annual rate of exacerbation to assess the response to treatment (▶ **Tab. 2**).

Expert consensus

Based on the evidence and their own practical experience, the authors propose the following specific criterion and thresholds:

- Measurement parameters: Rate of documented or patient-reported exacerbations per year requiring administration of ≥ 20 mg prednisolone over several days
- Thresholds:
  - Good response: Reduction of exacerbations by ≥ 75 % or 0 exacerbations
  - Response: 50–74 % reduction in exacerbations
  - Insufficient response: Reduction of exacerbations by < 50 % (▶ **Tab. 3**)

▶ **Tab. 2** Published criteria for evaluating the response of patients with severe asthma to biologics.

Non-response	Partial response	Response	Excellent response/ "super-response"	Reference
< 50 % reduction in severe exacerbations AND < 50 % reduction in OCS dose AND < 3 points improvement in ACT OR worsening of symptoms (i. e., increase in severe exacerbations and worsening of ACT) with phasing out of OCS		≥ 50 % reduction in severe exacerbations on average over the past 12 months AND ≥ 50 % reduction in OCS dose AND improvement in ACT by ≥ 3 points (MCID)		[18]
Discontinuation of IL5 therapy before 2 years have passed due to increase in symptoms OR decrease in FEV_1 OR increase in OCS consumption	Patients who meet neither the criteria for a non-response nor a super-response		No chronic OCS use, no short-term OCS therapy in the last 3 months, ACQ < 1.5, FEV_1 ≥ 80 % of target, FeNO < 50 ppb, and complete control of comorbidities (chronic rhinosinusitis, nasal polyps, chronic otitis, allergic rhinoconjunctivitis, and atopic dermatitis)	[15]
No relevant improvement in any of the three criteria or relevant deterioration in one criterion: (1) FEV_1 loss ≥ 150 ml, (2) drop in ACT ≥ 3 points, (3) any increase in OCS dose (duration > 2 weeks)		Relevant improvement in 1 of 3 criteria without worsening in any of the others (1) FEV_1 increase ≥ 150 mL, (2) increase in ACT score ≥ 3 points, (3) reduction in OCS ≥ 50 %		[13]
		≥ 50 % reduction in annual asthma exacerbation rate OR ≥ 50 % reduction in long-term OCS in patients requiring permanent OCS (after 48 weeks)	No exacerbations AND no long-term OCS	[16]
		Two of the following criteria are met: ▪ Improvement in FEV_1 (≥ 12 % or ≥ 200 ml) ▪ Reduction of the blood eosinophils (< 150 /µl or < 80 %) ▪ Improvement of the subjective state according to the patient's impression		[11]
			At least three of the following criteria are met (of which at least two main criteria): Major criteria ▪ No exacerbations ▪ Significant improvement in asthma control (≥ 2 × MCID) ▪ Discontinuation of OCS (or worsening of adrenal insufficiency) Minor criteria ▪ 75 % reduction in exacerbations ▪ Well controlled asthma (ACQ < 1.0 or ACT > 19) ▪ ≥ 500 ml improvement FEV_1	[19]
< 50 % reduction in severe exacerbations OR < 50 % reduction in OCS dose	Quantitative assessment by FEOS score (FEV_1, severe exacerbations, OCS use, symptom control)	Complete response: no severe exacerbations AND no OCS required AND ACT ≥ 20 AND FEV_1 > 80 % (OCS ≤ 5 mg prednisone equivalent for adrenal insufficiency, ACT < 20 for comorbidities, FEV_1 < 80 % for fixed bronchial obstruction)		[20, 21]

▶ **Tab. 3** Main criteria and thresholds for assessing the response to biologic therapy in patients with severe asthma.

Criterion	Measurement parameter	Threshold for good response	Threshold for response	Threshold for insufficient response
Reduction of exacerbations	Patient-reported exacerbations according to guidelines requiring OCS therapy over several days	0 exacerbations or reduction in exacerbations ≥ 75 %[1]	Reduction of exacerbations 50–74 %	Reduction of exacerbations < 50 %
Reduction of oral corticosteroids	Daily dose of long-term OCS therapy	OCS discontinuation or reduction ≥ 75 %[2]	Reduction of daily dose 50–74 %	Reduction of daily dose < 50 %
Improvement of asthma control	Asthma Control Test ACT	Improvement ≥ 3 points and score ≥ 20 or improvement ≥ 6 points	Improvement by 3–5 points and score < 20	No clinically relevant improvement (< 3 points)

Note: The criteria are for guidance and can be used as an aid in assessing the response to therapy. Individual assessment of patients remains essential.
[1] Avoiding exacerbation is an important treatment objective. In patients with a history of frequent exacerbations, a reduction of ≥ 75 % may already mean a good response. The cause of the remaining exacerbations should be identified.
[2] This parameter does not apply to patients who have an ACT ≥ 20 at the start of biologic therapy due to current high-dose OCS therapy and do not achieve an improvement > 3 points but still remain ≥ 20

Explanation

A reduction in exacerbations of at least 75 % per year was considered a target for a good response.

It should be taken into account that patients with frequent exacerbations per year also clearly benefit from a 50 % reduction (e. g., from 4 to 2), so a 50–74 % reduction in exacerbations is proposed as the threshold for response. Consequently, a reduction of less than 50 % is an insufficient response.

Second main criterion: Reduction of oral corticosteroids

According to the National Healthcare Guidelines for Asthma, biologics are the preferred add-on therapy in step 5; the use of oral corticosteroids as maintenance therapy should only be used as an add-on or as an alternative in justified cases [2]. The aim is to avoid side effects such as infections, cardiovascular events, diabetes, cataracts, osteoporosis, weight gain, and depression [2, 22, 23].

In practice, however, many patients with severe asthma still receive long-term OCS [23–26]. A good response to or need for OCS maintenance therapy has been shown to be a strong predictor of a therapeutic response to biologic therapies, e. g., shown for anti-IL5 receptor antibodies [27]. Phase 3 studies have shown that under biologic therapies it is possible to reduce or even completely discontinue previous maintenance therapy with OCS [28–30].

The MCID is also not validated for OCS reduction. Suggested thresholds for assessing the therapeutic response vary in the literature (▶ **Tab. 2**). In dedicated phase 3 OCS reduction studies, a mean OCS reduction of 50 % was achieved for mepolizumab, benralizumab, and dupilumab, however the extent of the potential OCS reduction was limited by the duration of the studies [28–30]. By contrast, in open-label studies, OCS could be reduced even further and often even resulted in complete discontinuation of therapy [31, 32].

Expert consensus

Based on the above evidence and their own practical experience, the authors propose the following criterion and thresholds:

- Measurement parameter: Daily dose of long-term oral corticosteroid therapy
- Thresholds:
  - Good response: Discontinuation of OCS or reduction of daily dose by ≥ 75 % (in case of adrenal insufficiency: max. 5 mg/d prednisolone equivalent or hydrocortisone as determined by endocrinology)
  - Response: Reduction of daily dose by 50–74 %
  - Insufficient response: Reduction of daily dose by < 50 % (▶ **Tab. 3**)

Explanation

A distinction should be made between patients with and without long-term OCS therapy when assessing the response to therapy based on the reduction in OCS. In patients on long-term OCS therapy, the goal is complete discontinuation of OCS; however, a large reduction (e. g., from 20 mg to 5 mg), particularly at high starting doses, should also be considered a success. Therefore, the authors considered a good response when the daily dose of OCS was reduced by ≥ 75 % or more, and a response when the daily dose was reduced by 50–74 %; an insufficient response was defined when the daily dose was reduced by less than 50 %.

Patients without long-term OCS therapy cannot improve further on this parameter, so this criterion cannot be considered for their response assessment (see also development of the score).

▶ **Tab. 4** Lung function as an important secondary criterion for evaluating the response to therapy.

Criterion	Measurement parameter	Threshold for good response	Threshold for response	Threshold for insufficient response
Improvement of lung function	FEV_1	Normalisation	Improvement	No improvement or deterioration
	Residual volume			
	Airway resistance			

Note: Improvement in lung function may not be achieved in all patients due to individual patient history. Therefore, a lack of improvement in lung function should not be considered as an exclusion criterion for a good response.

Although the primary goal is to completely discontinue OCS therapy, this is not always possible, such as in the presence of adrenal insufficiency, comorbidities (type 2 diseases, but also such as rheumatic diseases), or loss of asthma control. In this case, low-dose OCS therapy ≤ 5 mg/d prednisolone equivalent may be defined as a secondary treatment goal to keep the extent of OCS side effects acceptable. However, the authors believe that continued low-dose OCS therapy should be primarily accepted by the pulmonologist only if adrenal insufficiency is clearly the cause. On the other hand, if insufficient asthma control or a type 2 comorbidity is the cause, further opitmization of therapy should be sought, e. g., by switching to biologic therapy.

Third main criterion: Improvement of asthma control

Asthma control is essential for the assessment of the response as a measure of the limitations of the patient's daily life due to the disease. The authors agree that in all patients with severe asthma, asthma control should be evaluated regularly using questionnaires.

The most widely tool used in practice is the Asthma Control Test ACT (evaluation: 0–15 points: poor asthma control; 16–19 points: partial asthma control; 20–25 points: good asthma control) [33]. A difference of 3 points or more is considered clinically relevant [34]. Also for asthma control, different thresholds for the assessment of treatment response can be found in the literature (▶ **Tab. 2**).

Expert consensus

Based on the above evidence and their own practical experience, the authors propose the following criterion and thresholds:

- Measurement parameter: ACT
- Thresholds:
  - Good response: Improvement of ≥ 6 points (double MCID) or improvement of ≥ 3 points and endpoint ≥ 20 points (good control)
  - Response: Improvement of ≥ 3 points (MCID) and endpoint < 20 points
  - Insufficient response: Improvement of < 3 points (▶ **Tab. 3**)

Explanation

In the rare case of good asthma control at the beginning of the biologic, e. g., due to high-dose long-term OCS therapy, this parameter may be omitted from the assessment (calculation of the score using the two remaining parameters).

Additional patient-individual criteria

Additional criteria (see box) may play a role for individual patients and be supportive in assessing the response to therapy:

- Lung function should be measured and evaluated regularly. However, from the authors' point of view, no generally valid thresholds can be defined for this parameter because of the various individual constellations: For example, in patients with long-standing disease and irreversible airway remodeling, at best a small improvement in lung function can be expected from therapy, even if the overall response is otherwise quite satisfactory. In addition, coexisting COPD, for example, may prevent an improvement in lung function. Therefore, according to the authors, lung function is an additional criterion to the three main criteria that should be considered more qualitatively (normalised, improved, unchanged, deteriorated) (▶ **Tab. 4**). In this respect, it should be noted that not only the FEV_1 should be considered as a parameter but also the residual volume and airway resistance. These may better reflect the improvement in small airway function under biologics and indicate a significant improvement in some patients, even there is only a small change in FEV_1 [35].
- Quality of life can be assessed in different ways, ranging from patient-reported limitations of daily life to the collection of structured quality of life questionnaires such as the St. George's Respiratory Questionnaire (SGRQ), Asthma Quality of Life Questionnaire (AQLQ) or European Quality of Life 5 Dimensions questionnaire (EQ5D) which are rather laborious in daily practice.
- Patient preference and satisfaction is an important parameter, but it is difficult to objectify. It should therefore always be supplemented by objective criteria such as exacerbations, OCS use, and/or asthma control.
- A patient diary should ideally be kept by all patients with severe asthma, especially in the temporal context of initiating therapy with biologics.
- Missed days at work or school as well as limited physical performance place a heavy burden on many patients with

severe asthma. Therefore, on an individual basis, their reduction or improvement may be a key treatment objective.
- Comorbidities such as chronic rhinosinusitis with nasal polyps (CRSwNP) or atopic dermatitis may add to the patient burden and provide further information for phenotyping. For example, CRSwNP is typically caused by type 2 inflammation. Differential responses of asthma and the comorbidity may occur and may be a reason for switching to another biologic or, in rare extreme cases, for dual biologic therapy [36].
- Tolerability of the biologic therapy should be monitored regularly. Although all asthma biologics are generally well tolerated, side effects that require therapy may occasionally occur (e. g., local treatment for conjunctivitis with dupilumab) or, in rare cases, may lead to discontinuation of therapy.

PATIENT-SPECIFIC OPTIONAL ADDITIONAL CRITERIA
- Lung function
- Improvement of quality of life
- Patient preference and satisfaction
- Patient diary and peak flow diary
- Reduction missed days at work or school
- Physical capacity
- Comorbidities
- Tolerability

Development of a score to assess the response to therapy

In order to develop an easy-to-use score based on the three main criteria (reduction of exacerbations, reduction of OCS, and improvement of asthma control) that defines an overall "good response", "response" or "insufficient response", various methodologies such as a total score, calculating the mean, achieving 2 out of 3 criteria, and a visual score were discussed in collaboration with a consulting data scientist. A consensus proposal of calculating the mean from the three main criteria with the help of additional criteria for ambiguities or particular patient-individual constellations was chosen. The advantage of the mean over other methods is that a valid score result is obtained even when values are missing for a main criterion. This may be the case if one of the main criteria does not apply to individual patients (e. g., no OCS maintenance therapy) or one of the three main criteria are not available for evaluation (e. g., the ACT was not documented prior to initiation of the biologic).

Calculation of biologics asthma response score

To calculate the score, points are assigned for each main criterion as follows
- Threshold for good response reached: 2 points
- Threshold for response reached: 1 point
- Threshold for response not reached: 0 points

The mean is then calculated to assess the overall response to biologic therapy:
- Mean ≥ 1.5: good response
- Mean 0.5 to < 1.5: Response
- Mean < 0.5: Insufficient response

▶ **Abb. 1** and ▶ **Abb. 2** show the possible results for three/two applicable/documented main criteria.

Plausibility check

The newly developed score was tested for plausibility as an example in 30 patient cases in the expert group and then further evaluated in 229 patients by the Hannover Medical School (MHH). It was important to identify cut-off values and to translate the currently inconsistent approach into values. The current score is the result of the process.

As mentioned at the beginning, patients who respond but do not respond well are of particular interest, i. e., they are in the "yellow" area. Here, potentially further improvement can be achieved and a decision must be made on further therapy. For example, in patient 5 (▶ **Abb. 3**), the cause of the limited OCS reduction should be identified and it should be clarified whether the need for OCS is due to adrenal insufficiency or other comorbidities or whether asthma is the cause. This patient could possibly benefit from optimising therapy and switching to a different biologic.

Recommendations for the timing of assessment of response to therapy

The thresholds also required clarification as to when they should be reached after the start of therapy. Since patients are routinely seen on a quarterly basis, the authors believe that these patient contacts should be used to assess the response to biologic therapy. In this way, tolerability can usually be assessed after only 3 months. Often, the response is already evident at this point, based on symptom improvement, but it is too early to assess exacerbations and the need for OCS with sufficient certainty. Therefore, the first assessment of the response using the score should be made after 6 months. If the response is insufficient, therapy should be discontinued at this time (▶ **Abb. 4**) and switched to another biologic if necessary. In the case of an intermediate response, the decision whether to continue with the biologic or to change it is to be made on an individual basis. In some cases, it may be too early to properly assess the rate of exacerbation, e. g., if it varies seasonally or if the reduction of OCS therapy has not yet been completed. The final assessment should be made after 12 months if the biologic is continued.

Assessing the response after 4 months, as done in the clinical trials and incorporated into the guidelines, seems to the authors to be impractical in daily practice.

Therapy optimisation

If there is a response but not a good response, it should first be checked whether the therapy can be optimised. In doing so, it is important to consider the following points:

CRITERION_1	CRITERION_2	CRITERION_3		Average score	Assessment
2	2	2		2	Good response
2	2	1		1.7	
2	2	0		1.3	Response
2	1	1		1.3	
2	1	0		1	
1	1	1		1	
2	0	0		0.7	
1	1	0		0.7	
1	0	0		0.3	Insufficient response
0	0	0		0	

▶ **Abb. 1** Calculation of the mean score for three applicable/documented main criteria.

CRITERION_1	CRITERION_2	CRITERION_3		Average score	Assessment
2	2			2	Good response
2	1			1.5	
1	1			1	Response
2	0			1	
1	0			0.5	
0	0			0	Insufficient response

▶ **Abb. 2** Calculation of the mean score for two applicable/documented main criteria.

- Search for possible causes of remaining symptoms such as infections, insufficiently suppressed type 2 inflammation (detected by persistently elevated biomarkers), allergen exposure, comorbidities such as gastroesophageal reflux and chronic rhinosinusitis, smoking status, irritants, psychiatric factors
- Check adherence, check and, if necessary, improve the inhalation technique
- Review concomitant medication including dosage and adjustment if necessary

If there is no explanation for the sub-optimal response, the diagnosis should also be checked (e.g., differential diagnosis COPD/asthma, vocal cord dysfunction, cardiac disease) and the original asthma phenotyping should be re-evaluated.

Switching to an alternative biologic

Switching to another biologic is possible in the case of

- intolerability/biologic-associated undesirable effect
- insufficient response (“red”)
- response (“yellow”),

	Main criteria			Secondary criterion	Average score	Assessment
	Reduction of exacerbations	Reduction of oral corticosteroids	ACT improvement	Improvement of lung function		
Case 1	**100%** (4 → 0)	No OCS maintenance therapy	**+8** (16 → 24)	Stable in the normal range	2	Good response
Case 2	**67%** (3 → 1)	**100%** (10 mg → 0 mg)	**+ 18** (5 → 23)	No improvement	1.7	
Case 3	**100%** (10 → 0)	**100%** (20 mg → 0 mg)	**+4** (12 → 16)	No improvement	1.7	
Case 4	**75%** (4 → 1)	No OCS maintenance therapy	**+ 5** (11 → 16)	Improvement	1.5	
Case 5	**100%** (7 → 0)	**25%** (10mg → 7.5 mg)	**+9** (7 → 16)	Normalisation	1.3	Response
Case 6	**0%** (2 → 2)	**86%** (17.5 mg → 2.5 mg)	**+2** (20 → 22)	Stable in the normal range	1	
Case 7	**40%** (5 → 3)	No OCS maintenance therapy	**+ 3** (10 → 13)	Improvement	0.5	
Case 8	**0%** (1 → 2)	**64%** (20 mg → 7.5 mg)	**+ 2** (9 → 11)	No improvement	0.3	Insufficient response
Case 9	**33%** (3 → 2)	**20%** (12.5 mg → 10 mg)	**+1** (15→16)	No improvement	0	

▶ **Abb. 3** Example calculations and plausibility testing based on patient examples.

3 months after the start of therapy

Initial assessment of tolerability and response to therapy.
Stopping the therapy usually only in case of intolerance – otherwise continue the therapy.

6 months after the start of therapy

Initial assessment of the response to therapy.
Patients with good response: Continue therapy.
Patients with response: Check possibility of optimising therapy, continue or change therapy individually.
Patients with insufficient response or biologics-associated undesired effect: Stop therapy and switch if necessary.

12 months after the start of therapy

Final assessment of treatment response (including annual exacerbation rate).
Patients with good response: Continue therapy.
Patients with a response: Check possibilities for optimising therapy, switch if the old alternative is promising.
Patients with insufficient response or biologics-associated undesired effect: Stop therapy and switch if necessary.

▶ **Abb. 4** Procedure depending on the response to therapy.

1. If there are reasonable grounds for believing that the switch could result in further improvement. Here, biomarkers can provide clues: For example, if there are still exacerbations associated with increased eosinophils in the blood and/or sputum, a switch to (another) anti-eosinophilic therapy may be considered.
2. In case of patient dissatisfaction
3. If there is an additional comorbidity (such as nasal polyps) if this becomes an underlying health problem for patients as a result of the improvement of severe asthma. Attempting to treat both diseases with a single drug with a different antibody may be considered if there is a reasonable suspicion that the response to another biologic may result in further improvement of symptoms.
4. Specific patient needs

If an improvement in the response ("yellow") after 6 months appears likely as a result of switching biologic because of incomplete suppression of type 2 inflammation, then a change of therapy is appropriate at that time.

If therapy is continued and there is still no good response after 12 months, options for optimising therapy should be re-evaluated and treatment should be switched to another biologic if promising alternatives are available.

The response to the second biologic should generally be assessed analogously to the first biologic. If the previous improvement of a parameter can be maintained with the second biologic, this is also considered a response. The improvement in parameters should ideally be evaluated compared to the situation prior to the first biologic.

Role of biomarkers

Biomarkers play a secondary role in evaluating the clinical response to biologic therapy compared to clinical parameters. However, they are important in the choice of the initial biologic, as well as in the decision to switch, to another biologic. Comprehensive phenotyping of all patients with severe asthma is therefore essential before initiating biologic therapy, as well as in the absence of a good response. Assessment of biomarkers under therapy must take into account the different mechanisms of action that affect biomarkers in different ways. Measurement of eosinophils in the blood after initiating biologic therapy may confirm the underlying mechanism of action (decrease in eosinophil count for anti-IL-5, anti-IL-5 receptor, and anti-TSLP), on the one hand, and indicate a rare but relevant risk of side effects (increase in eosinophil count for anti-IL-4 receptor) on the other hand. An increase in FeNO levels after initiating biologic therapy, particularly with biologics that do not directly affect FeNO (anti-IL-5, anti-IL-5 receptor, anti-IgE), may be an indication of declining ICS adherence. The measured increase in serum IgE levels after starting omalizumab therapy reflects the formation of IgE-anti-IgE complexes and does not correspond to the target parameter of free or cell-bound IgE and is not indicative of a lack of effect or potential for side effects.

Various algorithms for selecting the initial biologic and switching in case of insufficient response have been published and are based mainly on the eligibility criteria as well as phenotypes and biomarkers that predict a response [17, 37, 38], as well as retrospective analyses on switching. In these retrospective analyses, a majority of patients benefited from switching from anti-IL5 to anti-IL5 R [39] or from anti-IgE/anti-IL5 /R to anti-IL4 R [13], if they did not fully respond to the current biologic. Controlled studies for direct comparison are not available.

Discussion

As the number of available therapies for severe asthma increases, the importance of selecting, evaluating and adapting biologic therapy becomes increasingly important. It is important for prescribing pulmonologists to assess the course of the disease during therapy. The BARS score presented here is intended to be simple, comprehensible and pragmatic.

The criteria presented here to assess the response to biologic therapy partially overlap with the recently proposed international criteria for asthma remission [40, 41]. Clinical remission as a concept describes the state of freedom from symptoms and exacerbations without the use of side-effect-laden therapies such as OCS, and also applies to patients with mild and moderate asthma treated with inhaled therapies. Assessment of the response to biologics and remission are complementary. Remission is the overarching goal; the assessment of the response to biologics takes into account the disease state of the patient with severe asthma prior to initiation of this therapy and the extent of improvement in the various parameters. An evaluation of the response is a prerequisite for deciding whether to continue or switch therapy in order to get as close as possible to the goal of remission.

The thresholds and the score were developed by experienced experts from both universities and practices.

While almost all of the proposals to date for evaluating the response to therapy have been designed to examine specific questions, a group of Spanish experts has recently published a proposal claiming general validity [20, 21]. A distinction is first made between non-response (< 50 % reduction in severe exacerbations or < 50 % reduction in OCS dose) and complete response (no severe exacerbations and no OCS and ACT ≥ 20 and $FEV_1 \geq 80\,\%$). If the patient falls into the “non-response” category, a switch in therapy is recommended; therapy should be maintained if the patient responds. If the patient is in between (“partial response”), the so-called FEOS score is calculated (**F**EV_1, severe **E**xacerbations, **O**CS dose and **S**ymptom control). Parameters are weighted differently and there are four or five thresholds depending on the parameter. Finally, the sum is formed with a possible total score of 0–100.

While the quantitative traceability-oriented methodology used in the development of this proposal is welcome, the calculation of the score does not seem simple in everyday life. The BARS presented here is much simpler and more practical because it is single-step, uses only values between 0 and 2, and can be used without a score calculator.

The score suggested here also has limitations: It presents a highly simplified picture of the response to biologic therapies. While adding additional criteria could provide a more accurate picture, it would not be applicable to every patient and would be less practical. Therefore, an individual assessment of each patient by the caregiver remains essential. Validation of the score has so far only been done on a limited number of cases from the centres where the authors work. Validation using a larger cohort is necessary and is currently in progress. The proposed score is based on the current healthcare situation, which shows that, according to the approval criteria of biologics, primarily patients with exacerbations and OCS maintenance therapy are treated with biologic therapies.

For some patients with severe asthma, it is already possible to achieve remission with biologic therapies today.

The aim of the scores proposed here to assess the response to biologic therapies is to provide a tool to objectively assess the response to therapy, thereby identifying patients in need of further therapy optimisation.

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Conflict of Interest

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