Definitions of non-response and response to biological therapy for severe asthma: a systematic review

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Shareable abstract (@ERSpublications)
There are no patient-centred composite measures of response to biologics for severe asthma. Single outcome measures are available but do not meet quality standards. A composite measure is required that is developed with patients. https://bit.ly/3FOJcXY

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Abstract

Background Biologics have proven efficacy for patients with severe asthma but there is lack of consensus on defining response. We systematically reviewed and appraised methodologically developed, defined and evaluated definitions of non-response and response to biologics for severe asthma.

Methods We searched four bibliographic databases from inception to 15 March 2021. Two reviewers screened references, extracted data, and assessed methodological quality of development, measurement properties of outcome measures and definitions of response based on COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN). A modified GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach and narrative synthesis were undertaken.

Results 13 studies reported three composite outcome measures, three asthma symptoms measures, one asthma control measure and one quality of life measure. Only four measures were developed with patient input; none were composite measures. Studies utilised 17 definitions of response: 10 out of 17 (58.8%) were based on minimal clinically important difference (MCID) or minimal important difference (MID) and 16 out of 17 (94.1%) had high-quality evidence. Results were limited by poor methodology for the

development process and incomplete reporting of psychometric properties. Most measures rated "very low" to "low" for quality of measurement properties and none met all quality standards.
Conclusions This is the first review to synthesise evidence about definitions of response to biologics for severe asthma. While high-quality definitions are available, most are MCIDs or MIDs, which may be insufficient to justify continuation of biologics in terms of cost-effectiveness. There remains an unmet need for universally accepted, patient-centred, composite definitions to aid clinical decision making and comparability of responses to biologics.

Introduction

According to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines, severe asthma is defined as asthma requiring treatment based on Global Initiative for Asthma (GINA) steps 4–5 for the previous year or oral corticosteroids for ⩾50% of the previous year either to prevent the disease becoming uncontrolled or disease which remains uncontrolled despite this therapy [1]. Even though severe asthma only affects 5–10% of the total population with asthma [1], it represents a significant socioeconomic [2–6], psychological [7, 8] and treatment [9] burden, and is also be associated with risk of mortality [10, 11].

Over the past decades, new biological drugs have demonstrated a positive impact on the lives of many patients with severe asthma by reducing the frequency of exacerbations and dose of oral corticosteroids, and by improving lung function [12–15]. Recently, in addition to total IgE, blood eosinophil counts and fractional exhaled nitric oxide (F_{ENO}) have been suggested as a guide to initiate anti-IgE treatment in adolescents and adults [16]. Furthermore, blood eosinophil counts have been used to select patients for anti-interleukin (IL)-5 in adults [16], and F_{ENO}/blood eosinophil counts for dupilumab in adolescents and adults [17]. Several studies have described the characteristics of patients who started biologics [18, 19] and the characteristics of responders to treatment [20–23]. It has been shown that some patients reached a "super-response" [24] or "partial response" [25], whereas others experienced a "non-response" [24] or even deterioration [26] of clinical and patient-reported outcome measures (PROMs).

Although many studies have measured responses to different biologics, there are no universally accepted criteria for what constitutes response, and the absence of guidance on criteria is reported as a high-priority research gap in both children and adults [27, 28]. Evidence about responder definitions is critical for understanding the effectiveness of treatment for patients [29], clinicians and regulatory bodies, such as the European Medicines Agency [30] and the Food and Drug Administration [31]. Minimal clinically important difference (MCID) [32] and minimal important difference (MID) [33] are often used for assessing responses; these are defined as the smallest relevant within-person change or group differences between treatments, respectively. According to the Food and Drug Administration report, it is useful to report intra-subject responses based on an *a priori* responder definition [31]. In November 2016, an ERS Task Force reached a consensus on a traffic-light system to classify patients as non-responders, intermediate responders or super-responders [34]. The Task Force suggested that patients need to be on biological treatment for at least 4 months before an initial assessment of response can be determined [34]. However, this proposal has neither been validated nor further developed.

Given the unmet need to use consistent definitions of response for paediatric and adult patients, we aimed to 1) synthesise evidence about definitions of non-response and response to biological therapy used in patients with severe asthma, 2) assess the quality of the evidence for these definitions, and 3) evaluate the development, measurement properties and quality of outcome measures as supporting evidence for the included definitions. We chose to restrict our systematic review to studies where definitions were methodologically developed, defined and evaluated. Comprehensive assessment of response in clinical practice and trials using prespecified consensus criteria should provide useful guidance for clinical decision making, allow comparison across studies, eliminate unnecessary treatment in patients with inadequate response and ensure that the high cost associated with biological therapies [35] is justified [36].

Methods

This was a systematic review conducted by the 3TR (Taxonomy, Treatment, Targets and Remission) [37] Respiratory Work Package members and external collaborators including academic clinicians, regulatory, patient and pharmaceutical representatives from across Europe. The study is registered at PROSPERO with identifier number CRD42021211249. Our aim was to look at response in severe asthma, but in anticipation that the evidence base would be limited, we initially included studies of all severities of asthma. However, given that there is evidence for definitions of response to biological therapy for severe asthma, the protocol was revised to restrict the systematic review to studies of severe asthma. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist has been used to structure this

article (supplementary appendix 1) [38]. The methods are briefly described here. Details are available in the supplementary material.

Search strategy

Four databases were searched (Embase (OVID), MEDLINE (OVID), CINAHL (EBSCOhost, Cumulative Index to Nursing and Allied Health Literature) and ISI Web of Science (Thomson Web of Knowledge)) using a search strategy developed on Embase (OVID) and then adapted for other databases (supplementary appendix 2). In summary, the search strategy was designed to identify papers focused on "asthma" AND "a biological therapy" AND "response/treatment outcome/minimal important difference". Databases were searched from inception to 15 March 2021. Additional references were searched through the references cited by the identified studies, systematic reviews, reviews, guidelines or highlighted by experts in the field.

Inclusion criteria

Studies were eligible for inclusion if they met the following criteria. 1) Population: children/adolescents (6 –17 years) and/or adults (⩾18 years) with a diagnosis of severe asthma. 2) Intervention: any biological therapy which was investigated and/or currently used for severe asthma. 3) Comparator: any comparator, including placebo or no comparator. 4) Outcomes: any definitions of non-response and response to biological therapy for severe asthma which were methodologically developed, defined and evaluated. Sole or a composite of clinical, patient-reported, biological and/or imaging outcome measures were eligible for inclusion. Additional evidence about these outcome measures including development (undertaken in studies of any severity of asthma) and validation (conducted in studies with biologics for severe asthma) was included. 5) Study types: randomised controlled trials, cross-sectional studies, controlled before-and-after studies, non-randomised controlled studies, case–control studies in humans, cohort studies and consecutive case series (with a minimum of 10 participants) published as full-text articles and letters published in English were eligible for inclusion. Additional evidence about development and validation of outcome measures was considered from qualitative and validation studies.

Exclusion criteria

The following were excluded from the analysis: systematic reviews and meta-analyses, narrative reviews, discussion papers, editorials, commentaries, case reports, animal studies, conference abstracts, studies not available in full form, studies published in a language other than English, unpublished material and non-asthma studies (*e.g.* viral bronchiolitis or viral-associated wheeze). Studies were also excluded if they only used outcome measures and definitions of response to assess treatment effectiveness or efficacy.

Study selection

All references were pooled and de-duplicated in Endnote version X9 (Thomson Reuters, Philadelphia, PA, USA) and subsequently uploaded to Rayyan (https://rayyan.qcri.org), where any remaining duplicates were removed. Titles, abstracts and full texts were screened independently by two reviewers (E.K. and A.R.) according to the predefined selection criteria and categorised as included, excluded or unsure. Any disagreements were resolved through discussion with a third reviewer (G.R.).

Data extraction, risk of bias assessment, quality and synthesis of the results

Data extraction was based on the COnsensus-based Standards for the selection of Measurement INstruments (COSMIN) guideline for outcome measures [39]. Definitions of the measurement properties provided by COSMIN are provided in supplementary table S1 and criteria for good measurement properties (GMPs) are provided in supplementary table S2.

Risk of bias of individual studies was assessed using the COSMIN checklist for PROMs [40, 41] and composite outcome measures (COSMIN risk of bias for non-patient-reported outcomes) [42]. Risk of bias for each measurement property in the validation studies was rated as very good, adequate, doubtful or inadequate. The certainty of evidence was assessed using the modified GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach [39, 41, 43]. Data extraction, risk of bias assessment and modified GRADE were completed independently by two reviewers (E.K. and A.R.). Any discrepancies were resolved by discussion or by a third reviewer (G.R.). A descriptive synopsis with summary data tables was produced and results were summarised using narrative synthesis. Detailed methods are provided in supplementary appendix 3. The results were reviewed and discussed within the Core Outcome Measures for Severe Asthma (COMSA) initiative [44] that included a multidisciplinary, European group of academic clinicians, regulatory, patient and pharmaceutical representatives. The group aimed to select the core outcome measure sets for paediatric and adult severe asthma.

Results

Description of studies

Our search strategy identified a total of 11 588 papers; 11 553 articles were excluded after title and abstract screening. The full text of 35 papers was assessed for eligibility, including 20 articles identified through review of citations. 13 papers were included in the systematic review, of which three were about development of the outcome measures [45–47], five were validation papers [48–52], and five reported development and validation data in the same paper [53–57] (figure 1).

Development and quality of definitions of non-response and response

The approach to development of definitions and their characteristics are shown in tables 1 and 2. Definitions were developed for three composite asthma outcome measures [52–54], three asthma symptom outcome measures [50, 51], one asthma control outcome measure [56] and one quality of life (QoL) measure [49]. The following methods of development were used: consensus [54, 56], anchor-based [49–52] and distribution-based [53] methods. 10 definitions measured response based on MCID [49, 50, 52] or MID [51, 53] and seven [51, 56] based on responder/non-responder levels. Omalizumab [49, 52, 53, 56], brodalumab [51], benralizumab [49, 54], reslizumab [49, 54] and mepolizumab [49, 50, 54] were predominantly used in these studies. Response was evaluated at different time-points, including as early as 4 weeks [49] and up to 60 weeks [52]. Most definitions were developed for adults [49–51, 53, 54], while three were for adolescents [50, 52, 53] and one was for children [52] with severe asthma. Quality of evidence for definitions of response was rated as "high" for all except "moderate" for the Asthma Severity Scoring System (ASSESS) [53] due to a lower number of patients taking biologics.

Development and content validity of the outcome measures

An overview of the developmental process and its quality are shown in table 2 and supplementary table S3. The developmental process was predominantly rated as "sufficient", while quality of evidence was mainly "very low" to "low", but "moderate" for the Severe Asthma Questionnaire (SAQ) [46, 55]. Three composite outcome measures were developed by physicians, including FEOS (forced expiratory volume in 1 s (FEV_1), exacerbations, oral corticosteroids, symptoms score) [54] for adults and ASSESS [53] which was adapted from the Composite Asthma Symptom Index (CASI) [57] for adolescents/adults and children with asthma, respectively. The Global Evaluation of Treatment Effectiveness (GETE) [56] scale was also developed by physicians. Only four outcomes were developed with patient input, including the SAQ [46, 55], Asthma Symptom Diary (ASD) [45], Asthma Symptom Utility Index (ASUI) [50] and Asthma Symptom Index (ASI) [47], which was adapted from the ASUI by excluding questions about medication side-effects. A summary of key instrument characteristics and feasibility is provided table 3 and supplementary table S4.

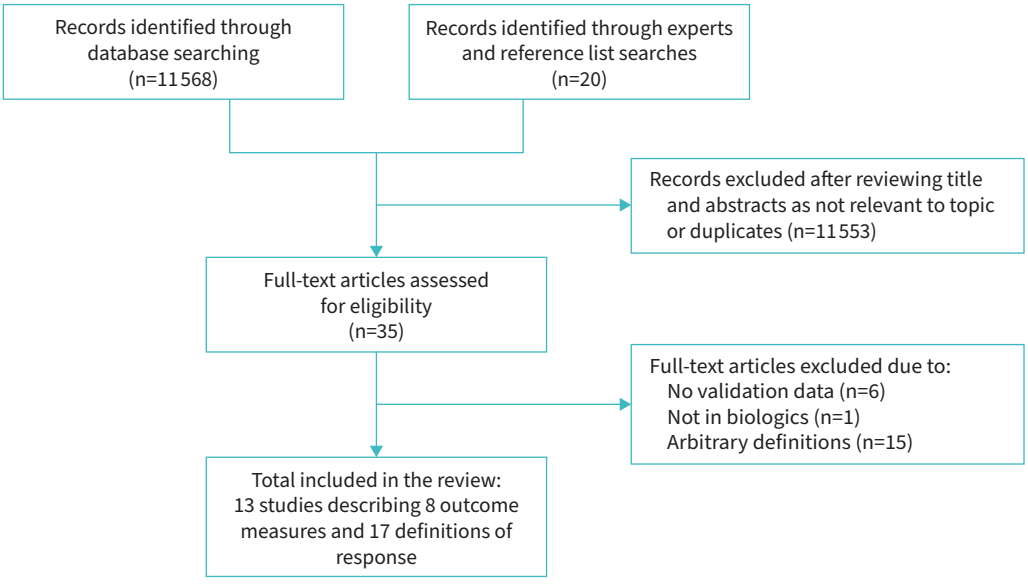

FIGURE 1 PRISMA diagram demonstrating study selection.

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TABLE 1 Characteristics of included studies

Study, year [ref.]	Scale	Study design	Patients (n)	Age (years)	Patient characteristics	Asthma severity (severe %)	Definition of asthma	Biological therapy
Composite outcome measures								
Fitzpatrick, 2020 [53]	ASSESS	Post-hoc analysis of 2 RCTs	562	44±0.7	Female 64.1%; FEV_1 74.2±0.9% predicted	Mild to severe (58.4%)	Modified ERS/ATS	Omalizumab (n=43)
Krouse, 2017 [52]#	CASI	Post-hoc analysis of RCT	419	10.8 (IQR 8–14)	Female 42.2%; FEV_1 92.0% predicted	Mild to severe (54.0%)	NAEPP	Omalizumab (n=208)
Perez de Llano, 2021 [54]	FEOS	NR	14	NR	NR	Severe (100.0%)	GINA step 5, ERS/ATS	Reslizumab (n=6), mepolizumab (n=5), benralizumab (n=3)
Asthma symptom outcome measures								
Shen, 2021 [50]	ASUI	Post-hoc analysis of RCT	497	51.0±13.6	Female 59.2%; FEV_1 58.8±15.7% predicted	Severe eosinophilic (100.0%)	ERS/ATS	Mepolizumab (n=269)
Shen, 2021 [50]	ASI	Post-hoc analysis of RCT	497	51.0±13.6	Female 59.2%; FEV_1 58.8±15.7% predicted	Severe eosinophilic (100.0%)	ERS/ATS	Mepolizumab (n=269)
Globe, 2019 [51]	ASD	Post-hoc analysis of RCT	417	47.3±13.6	Female 59.0%	Moderate-severe	Doctor-diagnosed	Brodalumab (n=283)
Asthma control outcome measures								
Lloyd, 2007 [56]	GETE	Post-hoc analysis of 3 RCTs	1380	12–76¶	NR	Moderate-severe	GINA, ATS, NHLBI	Omalizumab+
Asthma quality of life outcome measures								
Masoli, 2021 [49]	SAQ	Longitudinal cohort	110	49.0	Female 69.0%; FEV_1 67.0% predicted	Severe (100.0%)	ERS/ATS	Omalizumab (n=16), mepolizumab (n=26), benralizumab (n=62), reslizumab (n=2)

ACT: Asthma Control Test; ATS: American Thoracic Society; ASSESS: Asthma Severity Scoring System; ASUI: Asthma Symptom Utility Index; ASI: Asthma Symptom Index; ASD: Asthma Symptom Diary; CASI: Composite Asthma Severity Index; ERS: European Respiratory Society; FEOS: FEV_1, exacerbations, oral corticosteroids, symptoms score; FEV_1: forced expiratory volume in 1 s; GETE: Global Evaluation of Treatment Effectiveness; GINA: Global Initiative for Asthma; IQR: interquartile range; NHLBI: National Heart, Lung, and Blood Institute; NAEPP: National Asthma Education and Prevention Program; NR: not reported; RCT: randomised controlled trial; SAQ: Severe Asthma Questionnaire. #: definition was developed in mild to severe asthma and then evaluated in patients taking biological therapy; ¶: inclusion criteria are reported as the mean age of the participants is unclear; +: n=1380 patients from the randomised, placebo-controlled, double-blind studies were included in the analysis.

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TABLE 2 Definitions of non-response and response to biological therapy for severe asthma and their quality of evidence

Study, year [ref.]	Scale	Patient input in scale development	Time-point from baseline	Method of development of definition of response	Definition of response	Range of scores	GRADE
Composite outcome measures							
Fitzpatrick, 2020 [53]	ASSESS	No	12 months	Distribution-based method	MID 2 points	0–20 points (higher=worse)	⊕⊕⊕○[A]
Krouse, 2017 [52][#]	CASI	No	60 weeks	Anchor-based method	MCID 1 point	0–18 points (higher=worse)	⊕⊕⊕⊕
Perez de Llano, 2021 [54]	FEOS	No	NR	Delphi exercise, conjoint analysis	Response defined according to different thresholds for each outcome measure with respect to baseline; response ranges from 0 (worsening) to 100 (best)	0–100 points (higher=better)	⊕⊕⊕⊕
Asthma symptom outcome measures							
Shen, 2021 [50]	ASUI	Yes	12 weeks	Anchor-based method	MCID 0.07 to 0.11	0–1 points (higher=better)	⊕⊕⊕⊕
Shen, 2021 [50]	ASI	Yes	12 weeks	Anchor-based method	MCID −0.42 to −0.26	0–3 points (higher=worse)	⊕⊕⊕⊕
Globe, 2019 [51]	ASD[¶]	Yes	12, 24 weeks	MID (change −0.5 to −1.0 ACQ); responder (change ⩽ −1.0 ACQ)	Reported for 12 and 24 weeks: Mean 7-day score: MID −0.35 and −0.35; responder −0.54 and −0.68 7-day symptomatic days: MID −1.75 and −1.98; responder −2.34 and −3.22 Minimal symptomatic days-1: MID 1.97 and 2.16; responder 2.43 and 3.23 Minimal symptomatic days-2: MID 1.02 and 1.36; responder 2.31 and 2.56	0–4 points (higher=worse)	⊕⊕⊕⊕
Asthma control outcome measure							
Lloyd, 2007 [56]	GETE	No	28 weeks	Physician consensus	Responder (complete control; marked improvement of asthma); non-responder (discernible, but limited improvement in asthma, no appreciable change in asthma; worsening of asthma)	0–5 points (higher=better)	⊕⊕⊕⊕
Asthma quality of life outcome measure							
Masoli, 2021 [49]	SAQ	Yes	4, 8, 12 weeks	Anchor-based method	MCID (SAQ) 0.5 points; MCID (SAQ-global) 11 points	SAQ: 1–7 points; SAQ-global: 0–100 points (higher=better)	⊕⊕⊕⊕

ACQ: Asthma Control Questionnaire; ASSESS: Asthma Severity Scoring System; ASUI: Asthma Symptom Utility Index; ASI: Asthma Symptom Index; ASD: Asthma Symptom Diary; CASI: Composite Asthma Severity Index; FEOS: forced expiratory volume in 1 s, exacerbations, oral corticosteroids, symptoms score; GETE: Global Evaluation of Treatment Effectiveness; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; MCID: Minimal Clinically Important Difference; MID: Minimal Important Difference; NR: not reported; SAQ: Severe Asthma Questionnaire. [#]: definition was developed in mild to severe using anchor-based method and then evaluated in biologicals (MID was changed to MCID by the review team); [¶]: symptomatic days (defined as mean of the 10 ASD daily symptom items ⩾1, otherwise non-symptomatic day), minimal symptom days-1 (defined as mean of the 10 ASD daily symptom items ⩽1 and no single symptom item score>1, otherwise non-minimal symptom day-1) and minimal symptom days-2 (defined as no single ASD daily symptom item). Certainty of evidence was assessed using the GRADE approach [39, 41, 43]. The reason for downgrading was: A: indirectness.

TABLE 3 Summary of the characteristics of the outcome measures

	Recall period	Outcome measure content								
		ACT	Asthma control	Albuterol day/night	Asthma symptoms	Exacerbations	Asthma medications	mOCS	FEV_1	Quality of life
ASSESS [53]	Current (FEV_1, asthma medications); 4 weeks (ACT); 6 months (exacerbations)	X				X	X		X	
CASI [57]	Current (FEV_1, asthma medications); 2 weeks (symptoms, albuterol use); 2 months (exacerbations)			X	X	X	X		X	
FEOS [54]	Baseline to current (FEV_1 and mOCS); 4 weeks (ACT); 12 months (severe exacerbations)	X				X		X	X	
ASUI [50]	2 weeks				X					
ASI [50]	2 weeks				X					
ASD [45]	Current (morning and evening)				X					
GETE [56]	Baseline to current		X							
SAQ [46]	2 weeks									X

ACT: Asthma Control Test; ASSESS: Asthma Severity Scoring System; ASUI: Asthma Symptom Utility Index; ASI: Asthma Symptom Index; ASD: Asthma Symptom Diary; CASI: Composite Asthma Severity Index; GETE: Global Evaluation of Treatment Effectiveness; FEOS: FEV_1, exacerbations, oral corticosteroids, symptoms score; FEV_1: forced expiratory volume in 1 s; mOCS: maintenance oral corticosteroids; SAQ: Severe Asthma Questionnaire. The ASUI and ASI measure frequency and severity of asthma symptoms (cough, wheeze, shortness of breath and night-time awakening), while the ASD measures morning and evening symptoms separately (wheeze, shortness of breath, cough, chest tightness, night-time awakening or impairment of daily activities). The GETE measures effectiveness of biological treatment based on physician and patient view separately.

Risk of bias and quality of evidence for validation studies of outcome measures

Validation data including risk of bias are shown in supplementary tables S5–S7 and methodological quality of the outcome measures rated against criteria for GMPs is presented in table 4. Overall, almost all outcome measures had "inadequate" risk of bias due to lack of involvement of patients in the development, many measurement properties not being reported and none of the studies reporting cross-cultural validity including measurement invariance.

The GETE [56] scale has patient and physician versions which demonstrated high quality of evidence for construct validity, although there was a positive skew towards "complete control of asthma" and "marked improvement of asthma" possibly due to the ceiling effect. The CASI [57] showed insufficient responsiveness but "high" quality of evidence. Sufficient measurement properties were rated for ASSESS, including test–retest reliability, construct validity and responsiveness to change, while the quality was mostly "very low". The ASUI [50] and ASI [50] performed similarly and showed sufficient rating against GMP criteria and "low" to "high" quality. The SAQ [48, 49, 55] again showed sufficient properties and "very low" to "moderate" quality of evidence. Only responsiveness to change was evaluated for the ASD [51] as assessment of other measurement properties was not performed in patients taking biologics for severe asthma. The FEOS [54] scale only contains data about inter-rater agreement which was not possible to assess based on the COSMIN methodology.

Discussion

This study aimed to review the literature on definitions of response and non-response to biological therapy for severe asthma. To the best of our knowledge, the current systematic review is the first to synthesise methodologically developed, defined and evidenced definitions. We identified eight outcome measures: three composite outcome measures, three measuring asthma symptoms, one measuring asthma control and one measuring QoL. Studies utilised a variety of definitions of response criteria, mostly using MCIDs or MIDs where available and measured at different time-points for different biologics. Only GETE [56] defined a non-response, while FEOS [54] is a scale ranging from 0 to 100 (best), with no established cut-off for non-responders.

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TABLE 4 Evaluation of outcome measures against good measurement properties (GMPs) and their quality of evidence

	ASSESS [53]		CASI [57][#]		FEOS [54]		ASUI [47, 50]		ASI [50]		ASD [45, 51]		GETE [56][¶]		SAQ [46, 48, 49, 55][+]	
	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE
Relevance	+	⊕○○○^{A,B,C}	+	⊕○○○^{A,C}	+	⊕○○○^{A,C}	±	⊕⊕○○^{A,C}	±	⊕⊕○○^{A,C}	±	⊕⊕○○^{A,C}	+	⊕○○○^{A,B,C}	+	⊕⊕⊕○^{A}
Comprehensiveness	+	⊕○○○^{A,B,C}	–	⊕○○○^{A,C}	±	⊕○○○^{A,B,C}	±	⊕○○○^{A,B,C}	-	⊕○○○^{A,B,C}	+	⊕⊕○○^{A,C}	–	⊕○○○^{A,B,C}	+	⊕⊕⊕○^{A}
Comprehensibility	+	⊕○○○^{A,B,C}	±	⊕○○○^{A,C}	+	⊕○○○^{A,C}	+	⊕○○○^{A,B,C}	+	⊕○○○^{A,B,C}	+	⊕⊕○○^{A,C}	+	⊕○○○^{A,B,C}	+	⊕⊕⊕○^{A}
Reliability	+	⊕○○○^{A,C}	?		?		+	⊕⊕⊕○^{A}	+	⊕⊕⊕○^{A}	?		?		+[f]	⊕⊕○○^{A,C}
Construct validity[§]	+	⊕⊕○○^{A,C}	?		?		+	⊕⊕○○^{A}	+	⊕⊕○○^{A}	?		+	⊕⊕⊕⊕	+[f]	⊕⊕○○^{A,C}
Responsiveness	+	⊕○○○^{A,C}	–	⊕⊕⊕⊕	?		+	⊕⊕○○^{A}	+	⊕⊕○○^{A}	+	⊕⊕○○^{A}	?		+[f]	⊕⊕○○^{A,C}

GMPs for each measurement property were rated based on the COSMIN criteria [39, 41] as either sufficient (+), insufficient (–), indeterminate (?) or inconsistent (±, for development criteria only). Empty cells or indeterminate ratings indicate that the measurement property was not investigated or there is insufficient information. Structural validity, internal consistency, measurement error and cross-cultural validity are not shown in the table for all outcome measures due to the same reasons. For construct validity and responsiveness, the review team formulated *a priori* hypotheses about the expected relationships between an outcome measure and comparator instruments. Overall, ⩾75% of the pooled results for the measurement property were expected to meet the criteria in order to be classified as a sufficient rating [39]. ASUI: Asthma Symptom Utility Index; ASI: Asthma Symptom Index; ASSESS: Asthma Severity Scoring System; ASD: asthma symptom diary; CASI: Composite Asthma Severity Index; FEOS: forced expiratory volume in 1 s, exacerbations, oral corticosteroids, symptoms score; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; GETE: Global Evaluation of Treatment Effectiveness; SAQ: Severe Asthma Questionnaire. [#]: only external validation data were used for analysis as it was performed in a study with biologics; [¶]: physician and patient version of the GETE were graded similarly (assessment of the development was based on reviewer rating only); [+]: the SAQ is based on a formative model; therefore, there was no need to assess structural validity and internal consistency. [§]: as there is no gold standard in asthma, data about criterion validity were combined with construct validity; [f]: ratings apply to SAQ subscales (My Life, My Mind, My Body) and SAQ-global. Certainty of evidence was assessed using the modified GRADE approach as "high", "moderate", "low" or "very low" [39, 41, 43]. The reasons for downgrading were: A: risk of bias; B: inconsistency; C: indirectness.

One of the aims of the review was to assess the development and measurement properties of the identified outcome measures. Results were limited by "very low" to "low" quality of evidence for the development process, except for the SAQ [46, 55], and incomplete reporting of measurement properties for all outcome measures. Based on the COSMIN guideline, none of the outcome measures met all the quality standards. Only four outcome measures were developed with patient input, even though this is considered as a vital step in ensuring that the instrument is meaningful for patients. Responsiveness to change was rated as "low" to "very low", while definitions of response had "high" quality except for ASSESS [53].

Evaluation of therapeutic response in asthma has received increased attention with the introduction of biological treatments to improve disease treatment and precision management [58]. More than 70% of patients achieved good or excellent response to omalizumab based on GETE [59]; however, this relies on a single global measure to reflect the heterogeneous response to biological treatment. Thus, GETE does not discriminate the different effects of a treatment on different response areas, such as QoL, exacerbations, maintenance corticosteroid use and lung function. Two asthma symptoms questionnaires (ASUI and ASI [50]) were designed to assess cost-effectiveness of treatment, while the ASD [51] is a symptom diary and might impose too much burden on participants of biological therapy trials. The SAQ [55], which was developed with patient input, showed the best quality of evidence and was selected in the COMSA [44, 60].

Several composite outcome measures were identified. Neither the CASI [57] nor ASSESS [53] include a QoL domain, and the CASI [57] does not assess maintenance oral corticosteroid use, even though reduction in oral corticosteroid use and improvement of QoL have been shown to be the best indicators of response to treatment for patients with severe asthma [61]. The 2-point MID for ASSESS showed good specificity but poor sensitivity and the authors suggested that it should be interpreted with caution until more data are available [53]. The FEOS tool to quantify response [54] was developed for adults with severe asthma using novel methodology, but patients were not involved in the selection of outcome measures and it may not also represent the perspectives of international stakeholders. Unlike the COMSA initiative [44], the validity of the included outcome measures for severe asthma was not assessed and exclusion of aspects such as QoL may not represent a patient-centred approach.

This systematic review did not identify any studies which validated definitions of response to biological therapy using clinical outcome measures in patients with severe asthma. Some data are available from the consensus statements, *e.g.* the MID for FEV_1 is 0.20 L [13] or 10% improvement [62] and for F_{ENO} a reduction of $\geqslant$20% for values over 50 ppb (or $\geqslant$10 ppb for values lower than 50 ppb) should be used to indicate response to anti-inflammatory therapy [63]. While a published composite definition of exacerbation has been developed and validated in patients with severe asthma taking benralizumab, no MCID data are available yet [64].

Most outcome measures identified in the systematic review utilised MCIDs or MIDs to assess response, but we do not regard these definitions as interchangeable, *e.g.* in one paper the term MID was used when it would seem to be more appropriate to use MCID [52]. An improvement that patients might recognise as equivalent to the MCID with an inhaled asthma therapy may potentially be rated as less than the MCID in the context of high-cost biologics administered by injection [35, 36]. Also, to be regarded as cost-effective a biological therapy will demand a greater magnitude of response than a less expensive asthma therapy. A further critical variable may be the duration of response, given the case reports of secondary loss of response [65], *i.e.* the loss of response during the treatment over time despite an initial primary response [66, 67].

The concept of "super-responders" to biological treatment has emerged recently [24, 68]. In order to standardise the definition, a modified Delphi exercise among healthcare professionals has been conducted but there is a need to understand patient perspectives [69]. The rate of super-responders in patients prescribed anti-IL-5 depending on criteria ranges from 14% to 28% [24, 68, 70], forming a small but important group. Super-response should be the ultimate goal of treatment. However, patients who fail to achieve such a level of improvement may still benefit from biological therapies. Nevertheless, consideration should be given in such cases as to whether a different biologic may be more beneficial. Evaluation of a complete response, as in haematological disorders [71, 72], should be explored further in severe asthma even though only a very small percentage of patients experience remission [73].

Unfortunately, some patients with severe asthma do not respond to biological therapy and may even deteriorate. Differences in treatment response may be multifactorial, reflecting medicinal and/or subject variables including mechanisms of action, target, dose and interval of the biological drug or heterogeneity of asthma phenotypes [74]. For example, non-response might reflect differences in the pharmacokinetics of

biological drugs; indeed, monitoring plasma monoclonal antibody levels appears useful in various chronic diseases [75–77].

Overall, assessing the non-response and response after several months of treatment with biologics facilitates cost control by reducing the duration of ineffective therapy, and should enable better quality of care and patient experience by prescribing alternative treatments including switching to another biological if appropriate [78]. The latter is especially important given the rapidly increasing number of therapeutic options for patients with severe asthma [1, 16].

Strengths and limitations

This systematic review was conducted by a diverse group of academic clinicians, patient representatives, and regulatory and pharmaceutical representatives. This was a strength because it meant that definitions were considered on clinical and patient-centred grounds. A comprehensive search was conducted in four databases and provides a summary of the robust research. Rigorous methods were used including risk of bias assessment and GMPs based on COSMIN followed by the modified GRADE approach to rate the certainty of the evidence. Using transparent and validated COSMIN [39–41] methodology helped to standardise the quality assessment of outcome measures and reduce bias. Many studies were excluded as they used arbitrary definitions of response; only methodologically developed definitions and validated outcome measures were considered for inclusion in the systematic review. Lastly, all studies used data from a large number of paediatric and adult patients with severe asthma who were treated with a variety of biological therapies such as omalizumab, brodalumab, benralizumab, reslizumab and mepolizumab.

Nevertheless, we recognise several limitations. First, only studies published in English were included; however, we screened studies included in the guidelines, previous systematic reviews, references of identified articles and reviews, which made it highly unlikely that relevant studies were missed. Second, the search was conducted in 2021 as part of the development of the COMSA which was published in 2023 [44]. Third, we only searched the literature related to biological therapies and did not look at the evidence from response to non-biological asthma therapies. Biologics have different mechanisms of action, administration approaches, costs and potential adverse effects. Therefore, response criteria could differ with different patient views on what counts as a beneficial response given these considerations. However, it may be possible to also learn from the response to other therapies such as to oral and inhaled corticosteroids in severe asthma. Fourth, definitions of therapeutic response were assessed at different time-points, which might make it difficult to come to definitive conclusions about non-responders and responders. Moreover, COSMIN suggest using the lowest score counts method to assess measurement properties, meaning that having higher quality scores on some items of the checklist was not considered and only the “worst score” was reported. Lastly, it was not possible to run a meta-analysis due to low number of studies per outcome measure and only narrative synthesis was undertaken.

Policy implications and next steps

This systematic review aimed to inform clinicians, regulators and policy makers about the gaps and highlight heterogeneity of the definitions used. Even though the Asthma Control Questionnaire/Test and Asthma Quality of Life Questionnaire are widely used in phase 3 trials of asthma biologics and in clinical practice, definitions of response including MCID or MID have never been specifically assessed in biologics. Further research should aim to explore the identified definitions as primary and secondary outcomes in clinical trials including phase 2 and 3 efficacy studies and assess the MCID/MID of well-validated questionnaires in biological trials. There is also a need to methodologically develop patient-centred definitions of non-response and response to biological therapy for severe asthma for individual PROMs and clinical as well as a composite outcome measures. For example, based on COSMIN methodology for assessing the content validity of PROMs [41], patients should be asked about their relevance, comprehensiveness and comprehensibility. Engagement of patients is a crucial aspect of the development of outcome measures to meet their needs and preferences as well as to inform health decisions [79, 80].

Given the aforementioned, we are planning to develop definitions of non-response and response to biological therapies for paediatric and adult severe asthma trials and clinical practice based on the COMSA selected among key stakeholder groups, including patients with severe asthma [44]. We aim to standardise the definitions, which will allow better tailoring of individual treatment and be used in future clinical trials for documenting therapeutic response. Furthermore, looking at multiple dimensions of asthma such as exacerbations, QoL, asthma control and lung function in one single patient-centred composite would help to determine the correct sample size for future clinical trials, assist regulators in determining whether a new biological therapy is effective and identify predictors of treatment response. Use of such definitions will

also help in better understanding the applicability of novel biomarkers such as volatile organic compounds [81], peripheral blood gene expression [82, 83] and serum periostin [84] in the prediction and monitoring of response, which have been shown to be promising in biological treatment for severe asthma.

Conclusions

This systematic review is the first to evaluate the quality of evidence for definitions of response to biological therapy for severe asthma and measurement properties of associated outcome measures. There are several high-quality definitions available for use that are mostly based on MIDs or MCIDs, which might not be sufficient to justify continuation of biological therapy on cost-effectiveness criteria. Even though composite outcome measures are available and able to capture the multidimensional nature of severe asthma, none were developed with patient input and all lack a QoL component. Quality of evidence for the development and validation of the outcome measures was rated predominantly "low" and "very low", and none met all the methodological quality standards, highlighting an urgent unmet need. Therefore, the forthcoming 3TR project will aim to develop the definitions of non-response and response based on COMSA [44] with involvement of patient representatives and other key stakeholders. Future research will be needed to pilot these definitions in biological trials, and to address practical implications for policy makers, research and clinical practice. Knowing how to evaluate response to biologics using universally acceptable criteria would help in assessing the effectiveness of novel therapies, and improve clinical decision making and the care of patients with severe asthma.

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