Original Article

Development of a Tool to Measure the Clinical Response to Biologic Therapy in Uncontrolled Severe Asthma: The FEV_1, Exacerbations, Oral Corticosteroids, Symptoms Score

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What is already known about this topic? There is a lack of tools to quantify the response to monoclonal antibodies (mAbs) holistically in severe uncontrolled asthma patients.

What does this article add to our knowledge? We have employed a structured, transparent, participative, consistent, and legitimate methodology to develop a score to quantify the response to mAbs.

How does this study impact current management guidelines? This score reflects how much a given asthmatic improves with a mAb. It might be useful to guide therapeutic decisions in patients who achieve an intermediate response and in a head-to-head comparison of mAbs effectiveness.

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Abbreviations used
ACT- Asthma Control Test
FEOS score- FEV_1, exacerbations, oral corticosteroids, symptoms
FEV_1- Forced expiratory volume in 1 second
ICC- Intraclass correlation coefficient
mAb- Monoclonal antibody
MCDA- Multicriteria decision analysis
MCID- Minimal clinical important differences
SA- Severe asthma
SUA- Severe uncontrolled asthma

BACKGROUND: There is a lack of tools to quantify the response to monoclonal antibodies (mAbs) holistically in severe uncontrolled asthma patients.
OBJECTIVE: To develop a valid score to assist specialists in this clinical context.
METHODS: The score was developed in four subsequent phases: (1) elaboration of the theoretical model of the construct intended to be measured (response to mAbs); (2) definition and selection of items and measurement instruments by Delphi survey; (3) weight assignment of the selected items by multicriteria decision analysis using the Potentially All Pairwise RanKings of All Possible Alternatives methodology using the 1000minds software; and (4) face validity assessment of the obtained score.
RESULTS: Four core items, with different levels of response for each, were selected: severe exacerbations, oral corticosteroid use, symptoms (evaluated by Asthma Control Test), and bronchial obstruction (assessed by FEV_1 percent predicted). Severe exacerbations and oral corticosteroid maintenance dose were weighted most heavily (38% each), followed by symptoms (13%) and FEV_1 (11%). Higher scores in the weighted system indicate a better response and the range of responses runs from 0 (worsening) to 100 (best possible response). Face validity was high (intraclass correlation coefficient of 0.86).
CONCLUSIONS: The FEV_1, exacerbations, oral corticosteroids, symptoms score allows clinicians to quantify response in severe uncontrolled asthma patients who are being treated with mAbs.

Key words: *Asthma; Asthma management; Monoclonal antibodies; Severe asthma*

INTRODUCTION

Severe asthma (SA) affects approximately 5% to 10% of asthma patients and is associated with increased mortality. It generates greater health care costs than mild or moderate asthma.[1,2] However, because an assessment of SA is often based on subjects recruited from specialized centers that care for the most severely ill patients, and seldom on those from the community, the exact proportion of patients with severe uncontrolled asthma (SUA) remains to be definitely established, although it has been estimated at 3.9% in patients seen in hospital asthma units in Spain.[3]

Only a subset of SUA patients (40% to 70%) have increased airway type 2-high inflammatory biomarkers (sensitization to aeroallergens, blood and sputum eosinophils, exhaled fraction of nitric oxide.[4] Over the past decades, new add-on therapies have been developed and applied in this endotype, mainly monoclonal antibodies (mAbs) directed at blocking essential pathways in the type 2 inflammatory cascade.[5] However, clinicians are not provided with actionable tools to quantify the response to mAbs in SUA patients from a holistic perspective. In fact, virtually all clinical trials have been designed to evaluate the effect of mAbs on exacerbations or to quantify the reduction in systemic corticosteroid dose, but these outcomes do not meet all needs of SUA patients. In November 2016, a task force of experts on SA suggested a traffic light system to classify responses into one of three categories: super-responders, intermediate responders, and nonresponders. The experts that SA patients require treatment for at least 4 months before an initial assessment of response can be made. According to this approach, patients who are intermediate responders should either continue treatment for a year to assess response or be considered for a switch to an alternative mAb therapy.[6] Unfortunately, this proposal lacks specificity, requires further development, and does not consider the multidimensional and dynamic nature of asthma control (exacerbations, symptoms, physical limitation, quality of life, pulmonary function, and the need for systemic corticosteroids). Although individual response indicators are critical in randomized controlled trials, it might be more appropriate to group them in a composite measure to capture the true clinical condition of the patient more easily.[7] This problem has been solved in other diseases treated with biologics, such as rheumatoid arthritis. In that disease, the DAS-28 composite tool allows the clinician to measure disease activity in each subject and at different time points by including items from the physical examination, laboratory values, and patient perspective.[8]

Thus, the aim of this study was to develop a valid measurement tool to assist clinicians who care for SUA patients to better assess the response to mAbs.

METHODS

The methodological process for the development of a proposed score followed this sequence (Figure 1): (1) elaboration of the predicted model of the construct intended to be measured (response); (2) definition and selection of domains and measurement instruments; (3) weight assignment of the selected items; and (4) face validity assessment of the obtained score.

Identification of preexisting instruments: Systematic literature review

A methodologist conducted a systematic literature review to identify the response measures used in randomized controlled trials that evaluated the efficacy of different mAbs in SUA, to define potential domains to be included in the underdevelopment tool. The search was carried out on Medline through PubMed, IBECS, and MEDES databases, using Medical Subject Headings terms as well as key words and free terms.

Selection of domains and items

In a face-to-face meeting, the results of the review were presented to a national representative panel of specialists (five pneumologists and three allergists) with proven expertise in SA management. These experts developed the conceptual map of the response construct by using a nominal group technique with the assistance of the two methodologists (M.J.G.Y. and L.C.) and added potential domains (general concepts such as work productivity) and items (specific ways to estimate the concepts, such as questionnaires to measure the domain symptoms) to those previously selected.

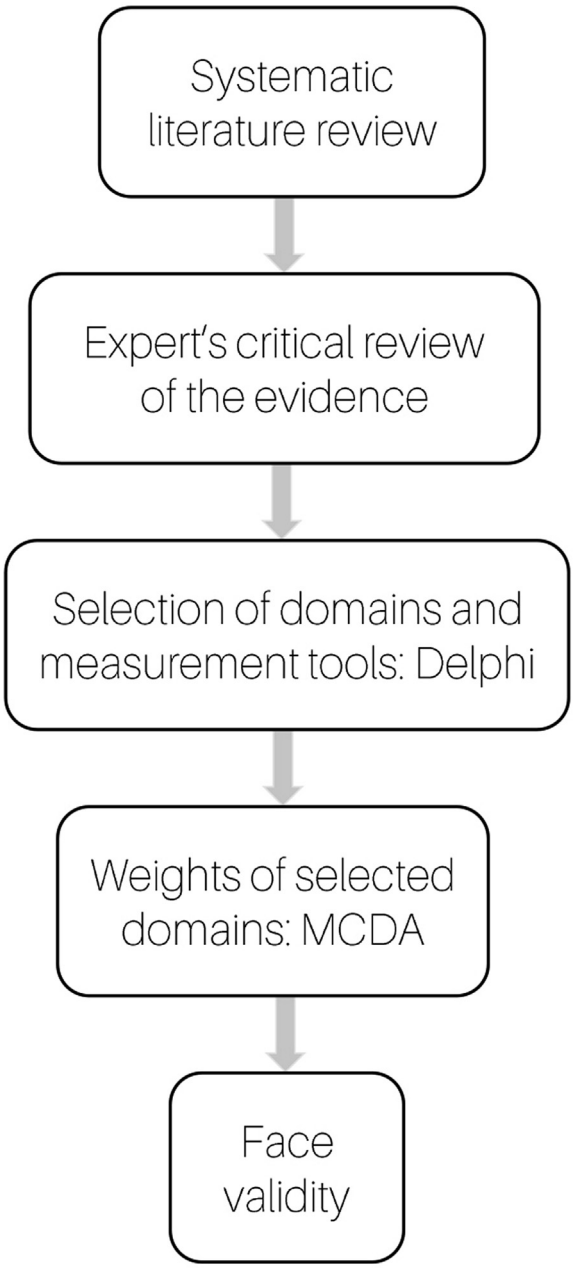

FIGURE 1. Phases of FEV_1, exacerbations, oral corticosteroids, symptoms score development. *MCDA*, multicriteria decision analysis.

Once the list of domains and items to assess response was generated, an online Delphi survey gathered the opinion of a larger group of pneumologists and allergists regarding the relevance of the proposed ones. A five-point Likert scale ranging from "not at all" to "completely agree" was used to determine the degree of convergence. Items with strong agreement (4 or 5) rated by greater than 80% of respondents were selected. This survey also assessed the agreement with different categories or levels of response for each specific item to establish the minimal clinical important differences (MCID), something necessary for the next phase. These levels of response were established considering the MCID for some of the variables (Asthma Control Test [ACT] and FEV_1), the global initiative for asthma definition of symptoms control, patients' future risk for exacerbations (history of one or more exacerbation in the previous year or low lung function), and previously published levels of response.

Weighting of items: Multicriteria decision analysis

The elaboration of composite response measures can be done using multicriteria decision analysis (MCDA), a statistical technique that calculates the differential weighting of a set of previously defined indicators (domains and items). The MCDA has been used to develop classification criteria and response scores for different diseases.[9-14]

Essentially, MCDA is a formal method to support decision-making involving the explicit weighting of different items and associated trade-offs among them. This process was carried out with the use of 1000minds (1000minds Ltd, New Zealand; http://www.1000minds.com), decision-making software based on the presentation of multiple changing scenarios to a panel of experts. With the items and levels of response resulting from the Delphi survey, the methodologists fed the software to create a set of hypothetical clinical scenarios that were then presented in pairs to the experts. Previously, the meaningless clinical situations were dismissed by the expert panel. Each element's response level was included separately in the survey; thus, 18 items were tested (eg, "Reduction between 50% and 100% in the number of exacerbations" was a tested item). At each pair of scenarios, participants had to choose which of the two situations reflected a better response to an mAb (Figure 2). The weights for each level of response were mathematically allocated by the Potentially All Pairwise RanKings of All Possible Alternatives method implemented in the 1000minds program, considering experts' responses to the survey. Every time a respondent chose "better response" in a clinical scenario designed to compare two options, the 1000minds software assigned more weight to the tested item. The resulting weights were finally expressed as a percentage.

Face validity

Although the face validity of this score (the degree to which users [in this case, the clinicians who prescribed the biologic] judge items of an assessment instrument to be appropriate to the targeted assessment objectives) could be guaranteed, because this tool was developed in a structured, transparent, consistent, and legitimate methodological way, it was further verified in a pilot study that compared how 1000minds software and an investigator (L.P.L.L.) ranked 14 real patients in terms of response. The agreement between the two raters was calculated using intraclass correlation coefficient (ICC).

RESULTS

Identification of preexisting instruments: Systematic literature review

The search strategies retrieved 82 and six articles in Medline and IBECS, respectively. No articles found in MEDES met established inclusion criteria, therefore, they were discarded. The most commonly used response criterion was exacerbations, defined as a worsening of asthma requiring treatment with systemic glucocorticoids (GC), increase of maintenance dose of oral GC 3 or more days, emergency visit less than 24 hours with systemic GC, or hospitalization 24 hours or more for asthma. Patient-reported outcomes were also frequently used as outcome measures or response criteria, specifically Total Asthma Symptom Score, Asthma Control Questionnaire, Asthma

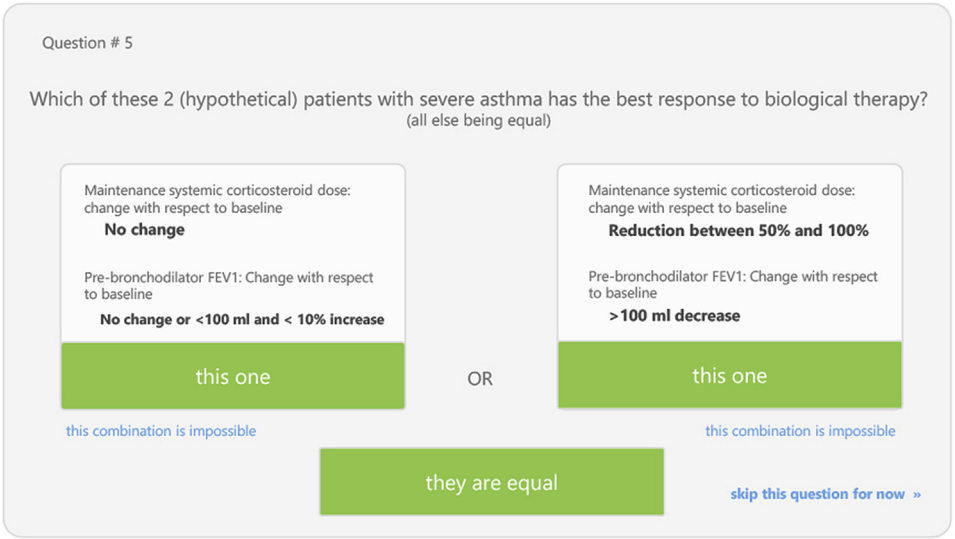

FIGURE 2. Example of pairwise comparisons generated by 1000minds.

Quality of Life Questionnaire, Global Evaluation of the Treatment Effectiveness, and Saint George's Respiratory Questionnaire. Finally, other outcome measures employed less often were oral corticosteroid reduction or withdrawal and changes in lung function tests.

Selection of domains and items: Nominal group and Delphi study

The nominal group defined the following domains and items for the construct "response": exacerbations, symptoms (measured by the ACT), quality of life (mini-Asthma Quality of Life Questionnaire), lung function (FEV_1), oral corticosteroid use, biological response (sputum eosinophils, nitric oxide in exhaled air), use of care resources, and work productivity (Work Productivity and Activity Impairment Questionnaire).

All of these items and the optional levels of response for each were then prepared into a Delphi survey that was sent to 88 professionals (58 pneumologists and 30 allergists), 68 of whom sent a response (77%). Agreement in the first round was as follows: exacerbation (98.4%), symptoms (98.4%), quality of life (83.6%), FEV_1 (95.1%), oral corticosteroid use (93.4%), biological response (83.6%), care resources (91.7%) and Work Productivity and Activity Impairment Questionnaire (60.0%). All domains except work productivity obtained a degree of agreement above 80%.

During a second face-to-face meeting, the expert panel decided to exclude the following items for further analysis: quality of life (for feasibility reasons, because it is not routinely collected in clinical records), biologic response (blood eosinophils and nitric oxide in exhaled air: owing to sufficient international consensus to determine changes in therapy; and sputum eosinophils: because there is no widespread availability), and use of care resources (included in the exacerbation's definition). Therefore, four core items were finally chosen: severe exacerbations (defined according to American Thoracic Society/European Respiratory Society guidelines as events requiring hospitalization or emergency department visit for asthma and systemic corticosteroids for 3 or more days),[15] oral corticosteroid use, symptoms (evaluated by ACT), and bronchial obstruction (assessed by FEV_1 percent of the predicted value). The experts also agreed on the best levels of response for each item (Table I).

TABLE I. Core domains and clinically relevant changes selected by Delphi survey

Domains	Level of response
Exacerbations	≥50% reduction No exacerbations
Symptoms control (by ACT)	≥3 points improvement in ACT ACT ≥20
FEV_1	≥100 mL and 10% ≥80% predicted value
Oral corticosteroid reduction	≥50% reduction Complete withdrawal

ACT, Asthma Control Test.

Weighting of items: MCDA

We invited 46 professionals from accredited asthma units (pneumologists and allergists) to complete the survey and participate in the MCDA; 41 completed the survey (89%). Table II shows the relative weights for each item derived from the analysis. Severe exacerbations and oral corticosteroid maintenance dose were weighted most heavily (38% each), followed by symptoms (13%) and FEV_1 (11%). Higher scores in the weighted system indicate better response; the range of responses runs from 0 (worsening) to 100 (best possible response).

Face validity

Agreement between raters was high, with an ICC of 0.86 (range, 0.69-0.94), which allows us to state that the designed tool has adequate face validity.

DISCUSSION

In recent years, new therapeutic options have become available in the form of mAbs. Although these novel biological drugs have shown promising results in SUA, it is evident that not all patients

TABLE II. The FEV1, exacerbations, oral corticosteroids, symptoms score

Criteria	Select	Points
Maintenance systemic corticosteroid dose: change with respect to baseline		
Increase‡	☐	0
No change§	☐	14
Reduction <50%	☐	24
Reduction of 50% to 100%	☐	29
Complete withdrawal	☐	38
Severe exacerbations: change with respect to previous 12 mo		
Increase*	☐	0
No change†	☐	11
Reduction <50%	☐	22
Reduction of 50% to 100%	☐	27
100% reduction		38
ACT questionnaire: change with respect to baseline		
ACT total score decrease	☐	0
<3 point increase	☐	5
≥3 point increase, but total score <20	☐	9
ACT ≥20	☐	13
Prebronchodilator FEV_1: change with respect to baseline		
>100 mL decrease	☐	0
No change or <100 mL and <10% increase	☐	5
≥ 100 mL increase and 10%, but <80%	☐	9
FEV_1 ≥80%	☐	11
Total score	☐	

ACT, Asthma Control Test; *FEV_1*, forced expiratory volume in 1 second.
Relative weights are converted into points for each item. Means, medians, and SDs of the relative importance of each item were reported as a percentage; the sum of each item's relative importance (weight) is therefore 100%. Higher scores in the weighted system indicate better response to monoclonal antibodies.
*Or at least one if the patient was free of severe exacerbations.
†Or if the patient was free of exacerbations and continued to have no severe exacerbations
‡Or if the patient was not receiving systemic corticosteroids and started the drug.
§Or if the patient was not receiving systemic corticosteroids and remained without them.

TABLE III. Highest possible score according to baseline clinical condition

Baseline condition	Maximal improvement
≥2 severe exacerbations Systemic corticosteroids ACT ≥20 (or <20) FEV_1 ≥80% (or <80%)	100
No severe exacerbations Systemic corticosteroids ACT ≥20 (or <20) FEV_1 ≥80% (or <80%)	73
≥2 severe exacerbations No systemic corticosteroids ACT ≥20 (or <20) FEV_1 ≥ 80% (or <80%)	76
No severe exacerbations No systemic corticosteroids ACT <20 FEV_1 <80%	49

ACT, Asthma Control Test; *FEV_1*, forced expiratory volume in 1 second.

respond equally well. Moreover, there is a lack of agreement about how to define a clinically valuable response or responder, what clinically relevant outcome measures are, and what the appropriate timing for assessing response should be. Pivotal clinical trials have defined responders to therapy using different criteria and different time points of evaluation, mostly addressing positive outcomes in exacerbation rate, symptoms, and the need for systemic corticosteroids use or lung function tests, assessed after 4 to 12 months of treatment.[6] We are unaware of prior studies focused exclusively on the development of a tool to measure response to mAbs in SUA. As mentioned, previous recommendations agreed on classifying patients into super-responders, responders, intermediate or indeterminate responders, and nonresponders.[6,16] However, these approaches lacked rigorous methodology, because they were based purely on expert opinion.

Using an MCDA method, we developed the FEV_1, exacerbations, oral corticosteroids, symptoms (FEOS) score to allow clinicians to quantify response to mAbs in patients with SUA. This score assigns relative weights to four items selected by expert consensus, covering all possible clinically relevant changes in patients' clinical condition after starting a biologic treatment. The higher the score, the larger the response to mAbs. However, the quantification of the achieved improvement depends on the baseline disease burden, and patients with poorer asthma control before initiation of mAbs have the potential to obtain higher scores after treatment compared with those with a better pretreatment clinical condition (Table III). In other words, the score does not provide an estimate of the level of asthma control attained after biologics therapy; rather, it reflects how much a given asthmatic improves. For instance, two hypothetical patients who experience a severe exacerbation after 12 months of biologic therapy, both of whom are treated with prednisone (10 mg/day), both of whom are symptomatic (ACT score of 17), and both of whom show residual bronchial obstruction (FEV_1 75% of predicted), can exhibit a different grade of response depending on the baseline condition. The FEOS score would yield 41 in one of these two patients if the pretreatment condition were characterized by an severe exacerbation, the use of 15 mg prednisone daily, an ACT score of 15, and FEV_1 75%, whereas the FEOS score would yield 65 in the other patient, with pretreatment clinical status defined by three severe exacerbations, the need for 20 mg prednisone, an ACT score of 7 and FEV_1 75%.

It might be interpreted as paradoxical that a patient with an ACT score of 19 at baseline would be assigned 13 points for increasing by just one point to 20, whereas a patient with a score of 12 at baseline would get only nine points for increasing by two to 16. On the other hand, a patient with a historical exacerbation at baseline would be assigned 38 points for having no exacerbations over the next 12 months, whereas a patient with five historical exacerbations who had only one over the next 12 months would be assigned only 27 points. This apparent disproportion could be explained by the fact that investigators who participated in the survey judged an increase in ACT score from 19 to 20 (just one point, but reaching the control level and consequently minimizing future risk) to be more relevant than an increase from 12 to 16 (reaching the MCID but not control). The explanation is the same for FEV_1. In the case of exacerbations, the experts considered it clinically more relevant to reach an exacerbation-free status (a situation that implies a low future risk) than merely reducing the number of exacerbations.

Another aspect worth comment is that it might seem counterintuitive to score above zero situations in which no change of clinical status is observed after biologic therapy. However, not assigning zero points to clinical situations in which no meaningful changes in the selected variables are detected can be considered a strength of the developed tool, because it makes it possible to sort out a floor effect that would impede scoring scenarios of clinical worsening, unless negative numbers (difficult to work with statistically and hard to interpret) are used.

Recently, in a 2-year follow-up real-life study, Eger et al[17] reported that 14% of patients were super-responders to anti-interleukin-5 biologics (with no residual disease manifestations), 11% were nonresponders (showing no meaningful clinical improvement or even worsening), and were 69% partial responders (those who did not fulfill the criteria of nonresponders or super-responders). To classify a patient as a super-responder or nonresponder is relatively easy. The real challenge for clinicians is whether to maintain or switch an mAb in cases of an intermediate or partial response, which is actually the most frequently found degree of response. In this scenario, the FEOS score can be helpful by quantifying how much the patient improved compared with pretreatment. It would be advisable to reach an experts' consensus on the acceptable amount of response to be achieved in an individual patient, but in the end, the final decision lies with the attending clinician, and there is a need for validated tools to help decision-making. On the other hand, because clinical trials to compare different mAbs head-to-head are not expected shortly, and it seems likely that most of the evidence will be generated through international registries, the FEOS score could quantify and compare the biologics' effectiveness.

Moreover, when considering the result of the score, time must be considered. Four to 6 months is a too short a period to evaluate the impact of mAbs on severe exacerbations, and corticosteroid withdrawal could have not been completed in this time frame.

Strengths and limitations

We have employed a structured, transparent, participative, consistent, and legitimate methodology to develop the tool. To the best of our knowledge, this the first score built for specifically measuring a response to mAbs in SUA. The obtained ICC value (0.86) reflects a good concordance between the mathematical method employed to estimate the degree of response and the judgment of a specialist on asthma who will use the score in clinical practice.

This study is a preliminary step toward implementing a validated scoring system to measure a response to mAbs in SUA patients. Moving forward, optimization of the FEOS score should include external validation by assessing the correlation of changes in the score and changes in a clinically valuable variable not included in the score (eg, quality of life) and its real-life applicability (eg, in an SA international registry).

We have developed a tool to quantify response in SUA patients who are being treated with mAbs. This instrument assigns relative weights to four clinically relevant items (severe exacerbations, oral corticosteroid dose, symptoms, and pulmonary function) that are available not only in specialized asthma units but also in primary care. Further investigation is needed to evaluate the correlation of this score with other meaningful outcome measures and to clarify its usefulness in real-life clinical settings.

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Author's contributions to the study: LAPLL was responsible for the design of the study, was part of the steering committee, participated in the Delphi and conjoint surveys, responsible for drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. ID, EMM, JDO, CA, CCS, JLGR, and BC formed the steering committee, participated in the Delphi and conjoint surveys, discussed the results and contributed to the final manuscript. LC and MJGY performed the systematic literature review, designed and analyzed the study and contributed to the final manuscript.

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