**Criteria to evaluate efficacy of biologics in asthma: a Global Asthma Association survey**

**Short title: Criteria to evaluate efficacy of biologics in asthma**

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**Abstract**

**Background**: Several biologics are now available as add-on treatment for severe asthma but, currently there are no universally accepted criteria to measure the response to these therapies. This survey aims to establish consensus criteria to use in practice for the initial evaluation of response to biologics after four months of treatment.

**Method:** Using Delphi methodology, a questionnaire including ten items was developed and validated by a 13-member panel of international experts in asthma. The electronic survey circulated within the INterasma Scientific Network platform, Global Asthma Association membership, contact list of the co-authors, national associations for specialists, and social media. For each item, five answers were proposed graduated from “no importance” to “very high importance” and by a score (A=2 points; B=4 points; C=6 points; D=8 points; E=10 points). The final criteria were selected if the median score for the item was ≥7 and >60% of responses accorded “high importance” and “very high importance”. All selected criteria were validated by the thirteen experts.

**Results**: Four criteria were identified to evaluate the efficacy of biologics in asthma: to reduce daily systemic corticosteroids dose by ≥50% (ideally complete withdrawal); to decrease the number of asthma exacerbations requiring systemic corticosteroids by ≥50%, (ideally no asthma exacerbation); to have no/minimal side-effects and to obtain asthma control according validated questionnaires. The consensual decision was that ≥3 criteria are needed to conclude a good response to biologics.

**Conclusions:** Specific criteria were defined by an international panel of experts and could be used as tool in clinical practice.

**Keywords :** asthma, biologics, criteria, efficacy, survey

**Introduction**

Severe asthma is defined as uncontrolled asthma despite optimized treatment by high-dose inhaled corticosteroids (ICS)- long acting beta2-agonists (LABA), good inhaler technique and adherence, and management of contributory factors or worsening control when high –dose treatment is decreased. Uncontrolled asthma includes poor symptom control and/or presence of frequent/serious exacerbations (≥2/year requiring oral corticosteroids or ≥1/year hospitalization). Despite a low prevalence (<5% of people with asthma), severe asthma places an important physical, mental, emotional, social and economic burden on patients1.

Several biologic therapies (e.g . anti-IgE, anti-IL5/R, anti-IL4R, anti-TSLP) were developed and are now available as add-on treatment for severe asthma with T2-inflammation. Most of them are able to reduce the burden from symptoms, exacerbations and systemic corticosteroids toxicity1,2. Current guidelines recommend the instauration of a biologic therapy for patients with exacerbations or poor asthma control despite maintenance oral corticosteroids (OCS) or at least high-dose ICS-LABA, who have an allergic background or eosinophilic phenotype with assessment of the therapeutic response at 4 months. Although the eligibility criteria are very well defined for each biologic therapy, currently, there are no universally accepted criteria to measure the response to biologics. The Global Initiative for Asthma (GINA) suggests to consider exacerbations, symptom control, lung function, side-effects, treatment intensity (including OCS), and patient satisfaction for the assessment of the response to biologics1.

Different criteria have been used in clinical trials that evaluated the efficacy of biologic therapies. A study used as criteria of response at 4 months the reduction with ≥50% of the exacerbations rate and for patients requiring OCS the decrease by ≥50% in prednisolone dose3, while another improvement of the Asthma Control Questionnaire (ACQ) score by ≥0.5 from baseline or reduction in maintenance OCS dose of ≥25% 2. Usually, the term of « super responders » were used to define patients who meet all criteria of response2-4. Two other studies evaluated the response to biologics at 12 months of treatment, one by using the minimal clinically important difference (MCID) for exacerbations, OCS maintenance, lung function and symptom control improvement and another the Standardized Measure to Assess Response to Therapy (SMART), a complex tool involving physician’s subjective opinion, six objective parameters and the combination of both modules5,6.

The absence of well-defined criteria for the assessment of response to biologics and the high heterogeneity of those used in different studies allowed us to conduct a survey by using a questionnaire validated by thirteen experts of InterAsma-The Global Asthma Association. Ten items were included targeting the assessment of asthma control, exacerbations rate, OCS use, lung function and side-effects. The objective was to establish five criteria to use in practice for the initial evaluation of response to biologics after four months of treatment.

**Method**

**Delphi group panel members**

We convened an international Delphi group consisting of a 13-member panel of experts in asthma, including seven pulmonologists, four allergologists, one Internal Medicine specialist and one Pediatrician. Panel members were selected on the basis of their clinical expertise, prior published research, expert recommendations, and membership in Global Asthma Association.

**Delphi surveys**

We applied the Delphi technique, a consensus method used to determine the extent of agreement on an issue by asking experts to answer survey questions in iterative rounds7. To reduce the number of rounds in our study, the items of the questionnaire were generated from the literature rather than from an initial round of the Delphi technique. A literature review of the PubMed database for English articles published from the 1st January 2019 to 30th June 2022 by using the association of terms « response to biologic therapy » and « severe asthma » has been done by the primary investigator to generate the questionnaire. Following the findings in the literature and the current recommendations1, ten items were proposed to assess the response to biologic therapies in patients with severe asthma at 4 months of treatment by including two items for the symptoms control, two items for the severe exacerbation rate, two items for the improvement of the lung function, two items for the OCS withdrawal, and two items for the side-effects (Appendice).

Two consecutive rounds were done into the expert’s panel for the validation of the questionnaire. In each survey round, panel members were asked to rate each item as a level of agreement on a scale from 0 « total disagreement » to 9 « total agreement » for the inclusion in the final questionnaire7. In the first round, the experts were invited to suggest additional items, recommend modifications to existing items and to submit free-text comments to clarify their response to every item. A median value ≥7 was considered as appropriate to keep the item in the final questionnaire. All the suggested items were accepted by the experts. In the second Delphi round, the experts were asked to re-rate their agreement for each item from the modified questionnaire. All the items were validated with a median score ≥7 and included in the electronic survey.

The electronic survey was circulated within the INterasma Scientific Network –INESNET platform (109 members, mass email from the headquarters), Global Asthma Association membership (>500 members, mass email from the headquarters), contact list of the co-authors, national associations for specialists, and social media (Facebook and Twitter) between July and August 2022, and evaluated by the co-authors. The invitation email contained an encouragement to spread the survey in the membership social network. The outreach on social media has not been quantified.

**Statistical analyses**

Statistical analysis was performed using the SPPS program version (SAS Institute, Cary, NC, USA). Qualitative variables in descriptive analysis are expressed as number and percentage. Quantitative variables are presented as mean ± standard deviation (SD) and median. For each item of questionnaire, a descriptive analysis has been done according to the answers but also a scoring of them (A = 2 points; B = 4 points; C = 6 points ; D=8 points ; E=10 points) in order to compare two by two the items concerning the same question : symptoms control (Q1&2), exacerbation rate (Q3&4), lung function (Q5&6), OCS withdrawal (Q7&8), and side-effects (Q9&10) and to choose the final criteria. Comparisons of quantitative values were performed using TTEST and between qualitative values by using Fisher test. Spearman’s test was used to assess correlations between responses. The limit of significance was *p* < 0.05.

**Derivation and consensual validation of the final criteria**

The results were analysed by the panel of experts in order to validate the final criteria to propose for the evaluation of the efficacy of biological therapies in patients with severe asthma in practice at 4 months of treatments. The predefined conditions necessary for the selection of criteria were a median score ≥7 and >60% of responses “high importance” and “very high importance”. All selected criteria were validated by the thirteen experts.

**Results**

One hundred thirty-two questionnaires were completed by specialists in asthma across the world (from 31 countries). The top five of countries according the number of participants included France (19 participants), Greece (17 participants), Argentina (16 participants), Italy (13 participants), and Mexico (11 participants). The mean age of participants was 55±11 years and there was a predominance of males (64%). More than half of participants were pulmonologists (53%) and near one third of them allergologists (32%). The other specialities were less represented (Table 1). Forty-eight percent of participants chose the option to be involved in the scientific dissemination of results.

The first item (Q1) concerns MCID in the improvement of symptoms control assessed by validated questionnaires: Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT)1. The median score for this item was 8 [2; 10] and the mean score 7.1±2.2. Nineteen percent of participants accorded a « very high importance », 34% « high importance », 32% « moderate importance », 11% « low importance », and 4% « very low importance » to this item (Table 2). The second item (Q2) evaluates the importance to obtain the status of « well-controlled » asthma according to ACQ and ACT scores1. The median score was 8 [2; 10] and the mean score 7.8±1.9. The distribution of the answers was: 28% « very high importance », 42% « high importance », 23% « moderate importance », 5% « low importance », and 2% « very low importance ». The comparison of these two items found not significant difference for the distribution of the answers (p=0.306) (Figure 1A), but significant difference concerning the scores (p=0.005) (Table 2) with a higher mean for the second item despite equal medians.

The next two items assess the exacerbation rate requiring OCS use. For the reduction of the rate by 50% (Q3), the median score was 8 [2; 10] and the mean score 8.6±1.5. The analyses of the answers showed : 45% « very high importance », 43% « high importance », 10% « moderate importance », 2% « low importance », and 1% « no importance » (Table 2). Concerning the objective « no exacerbation » (Q4), there were 57% of answers for « very high importance », 31% for « high importance », 9% for « moderate importance », 2% for « low importance », and 2% for « very low importance ». The median score was 10 [2 ; 10] and the mean score 8.9±1.7. No significant differences were found when these two items were compared (for the distribution of the answers, p=0.749; for the scores, p=0.079) (Figure 1B, Table 2).

Concerning the MCID for improvement of forced expiratory volume in 1 second (FEV1) based on patient perception (Q5)8,9, the distribution of the answers showed 5% for «very high importance», 22% for «high importance», 52% for «moderate importance», 19% for «low importance», and 2% for «very low importance». The median score was 6 [2; 10] and the mean score 6.2±1.7 (Table 2). For the improvement of the FEV1 by 12% and 200 mL (Q6), usually considered as significant in asthma1, 11% of participants accorded a « very high importance », 35% « high importance », 30% « moderate importance », 20% « low importance », and 5% « very low importance ». The median score was 6 [2; 10] and the mean score 6.3±2.4. No difference was found for the comparison of scores for Q5 and Q6 (p=0.216), but the distribution of the answers was significantly different (p=0.027) (Table 2, Figure 1C).

For the reduction of daily OCS dose by 50% (Q7), 45% of participants accorded « very high importance », 40% « high importance », 11% « moderate importance », 2% « low importance », and 2% « very low importance ». The mean score was 8.5±1.8 and the median score 8 [2; 10] (Table 2). Sixty-eight percent of participants chose « very high importance » for the achievement of complete withdrawal of OCS use at 4 months of treatment (Q8), 23% « high importance », 3% « moderate importance », 5% « low importance », and 2% « very low importance ». The median score for this question was 10 [2; 10] and the mean score 9.0±2.0, significantly higher values compared to those obtained for Q7 (p=0.048). Even the distribution of the answers for these two questions was significantly different (p=0.022).

The last two items evaluated the side-effects. For the item « no side-effects » (Q9), 37% of participants chose « very high importance », 39% « high importance », 17% « moderate importance », 4% « low importance », and 3% « very low importance ». The distribution of the answers for the item « minimal side-effects » (Q10) was similar : 36% for « very high importance », 41% for « high importance », 13% for « moderate importance », 9% for « low importance », and 2% for « very low importance » (p=0.896) (Table 2, Figure 1E). No significant difference was found when the scores were compared because the median was 8 [2; 10] for both items, and the mean score 8.1±2.0 for Q9, respectively 8.0 ± 2.0 for Q10 (p=0.756) (Table 2).

The top 10 ranking according the association of the answers « very high importance » and « high importance » is represented in the Figure 2A : Q8 – complete withdrawal of daily OCS use (91%), Q4 – no asthma exacerbation requiring OCS (88%), Q7 – reduction of daily OCS dose by 50% (88%), Q3 – decrease of asthma exacerbation number requiring OCS by 50% (86%), Q9 – no side-effects (77%), Q10 – minimal side-effects (77%), Q2 – achievement of asthma control (71%), Q1 – significant improvement of asthma control (53%), Q6 – increase of FEV1 by 12% and 200 mL (46%), and Q5 – augmentation of FEV1 by 10% (27%). It is interesting to note that the items 8 and 4 had more than half of answers as « very high importance » (68%, respectively 57%) (Figure 2B).

Using our predefined rules (the cut-off of ≥7 for the median score and >60% of responses “high importance” and “very high importance” on the top 10 ranking) we chose the first five items and generate finally four criteria (Figure 3) for the assessment of biologic therapies efficacy in severe asthma at 4 months of treatment that were validated for all the members of the panel. The consensual decision was that at least 3 criteria are needed to conclude a good response to biologics.

There was a significant direct relationship between responses to Q1 and Q2 (ᵨ=0.42), Q1 and Q3 (ᵨ=0.23), Q2 and Q3 (ᵨ=0.24), Q2 and Q4 (ᵨ=0.28), Q2 and Q8 (ᵨ=0.30), Q3 and Q7 (ᵨ=0.54), Q3 and Q10 (ᵨ=0.31), Q5 and Q6 (ᵨ=0.57), Q5 and Q9 (ᵨ=0.27), Q5 and Q10 (ᵨ=0.27), Q6 and Q9 (ᵨ=0.37), Q7 and Q8 (ᵨ=0.22), Q7 and Q9 (ᵨ=0.18), Q7 and Q10 (ᵨ=0.27), as well as Q9 and Q10 (ᵨ=0.38, all p<0.05, Figure 4).

**Discussion**

This survey documents the criteria considered as relevant by specialists across the world to assess the efficacy of biologic therapies available for the treatment of severe asthma, and accordingly proposes four of them as an easy tool to use in clinical practice. The final criteria highlight the importance accorded by specialists to the reduction/withdrawal of daily OCS use, the significant decrease of severe asthma exacerbations rate at four months of treatment, the good tolerability, and the achievement of asthma control.

The most important objective for the specialists treating patients with severe asthma seems to be the complete withdrawal of daily OCS (item with 68% answers « very high importance », respectively 91% when the answers « very high importance » and « high importance » are associated). This is an expected result in light of the high risk to develop steroid-related adverse effects (3.6-fold greater with long-term OCS use than with no use): sleep disturbances, adipose tissue redistribution, weight gain, dyslipidemia with cardiovascular risk, hypertension, diabetes, osteoporosis, myopathy, peptic ulcer, adrenal insufficiency, infections, mood, ophthalmological and skin disorders10-12. Despite the fact that most biologic therapies showed an OCS-sparing effect, the complete withdrawal at 4-6 months of treatment was achieved in limited groups of studied populations (e.g. omalizumab was able to decrease the proportion of patients receiving OCS by 32% compared with baseline, mepolizumab by 29%, benralizumab by 52%, and dupilumab by 52%)13-16. In addition, the rapid decrease of the daily OCS dose could not be possible in the event of adrenal insufficiency17. So a more realistic objective could be the reduction of daily OCS use by 50%. This item is issued from previous clinical trials that studied the efficacy of biologic therapies in severe asthma16,18. This objective has been chosen by 88% of participants to our survey and achieved in practice for more than half of patients receiving biological therapies for 4-6 months in clinical trials (mepolizumab 54%, benralizumab 66%, dupilumab 80%) 15,16,18.

According to the results of our survey, the second objective for the participants when they prescribe biotherapies for severe asthma is to reduce the number of asthma exacerbations requiring OCS with 88% of answers in favor to « no exacerbation » and 86% whishing the decrease by at least half of their number. As the precedent objective, this is another important step to achieve in the OCS-sparing strategy in severe asthma. It is now well established that not just the continuous exposure to OCS has deleterious effects with a dose-dependent relationship, but also the intermittent administration ≥4 times/year is associated with an increased risk for experiencing new adverse effects within the year (odds ratio 1.29)19-22. All biotherapies showed a positive impact on the asthma exacerbation rate. Omalizumab reduced the risk of severe exacerbations by 81% at 16 weeks of treatment (p<0.01), mepolizumab by 53% at 32 weeks of treatment (p<0.001), benralizumab by 49% at 24 weeks of treatment (p<0.001), and dupilumab by ≥46% at 52 weeks of treatment (p<0.001)13,23-25. A high positive correlation was found between the answers for reducing the asthma exacerbation rate and decreasing daily OCS dose by half.

The side-effects represent a mandatory criteria in the evaluation of the continuation of a treatment and an important field in the asthma management cycle for personalized care1. More than three quarters of participants to our survey chose « no side-effects » and « minimal side-effects » suggesting that the specialists prescribing biotherapies accord a high importance to the good tolerability of these treatments.

Regarding the assessment of asthma control by validated questionnaires ACQ or ACT, the achievement of symptom control (Q2) was considered the most important by participants than the significant improvement of the score at 4 months of treatment compared to baseline (Q1) (71% vs 53%) and the median scores were significantly different. Although assessment at 4 months may be insufficient in some patients to properly assess their response to biologics, almost all biotherapies significantly improved asthma control at 4-6 months of treatment. Omalizumab decreased the ACQ score at 16 weeks of treatment by -1.14 [1.4-0.89], mepolizumab at 32 weeks by −0.94±0.07, benralizumab at 24 weeks by least square mean -1.66, and dupilumab at 24 weeks by -1.40 ± 0.04 13,23-25.

The improvement of FEV1 was not considered a priority by the participants in our survey with less than half of answers for the association « high importance » and « very high importance ». It is interesting to note that 52% of participants accorded « moderate importance » for the improvement of FEV1 by 10% considered as MCID based on patient perception8,9.

The ranking obtained in the present survey is in line with the results from a recent systematic review realized on the use of biological in severe asthma that found a high certainty for the reducing of the severe asthma exacerbations rate and OCS use by these therapies, but a modest effect on asthma control26.

This survey allowed us to establish four criteria considered the best by respondents to evaluate the efficacy of biotherapies at four months of treatment. These criteria include the reduction of daily OCS use to complete withdrawal, the decrease of severe asthma exacerbations rate, the satisfactory tolerability with minimal or no side-effects and the achievement of asthma control according to ACQ or ACT score. All these criteria were validated and approved by the panel of experts. The consensual decision was that at least three criteria are needed to conclude a good response to biological therapy. We can also suggest that a « super-response » could be defined in the presence of all four criteria. To our knowledge, this is the first study reporting well defined criteria preferred for the assessment of the efficacy of biotherapies in practice. An important limitation of the report is represented by the fact that our aim was to find five criteria while we obtained just four.

Our survey highlights the criteria considered as important and very important by specialists from across the world for the assessment of the efficacy of biologic therapies in severe asthma. Based on the results of this survey, four criteria were defined by the international panel of experts and are now ready for use as tool in routine clinical practice but also in research studies. The ideal time of assessment of biologics remains however to be better defined, particularly in the context of partial responses, and this for each biologic, so more research is needed on optimal time and mean of assessment of these responses. Furthermore, the use of one or more biomarkers in response assessment should be also studied.

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|  |  |
| --- | --- |
| 1. To improve the ACQ score by 0.5 points or the ACT score by 3 points   A. no importance  B. low importance  C. moderate importance  D. high importance  E. very high importance | 1. To obtain an ACQ score <1.5 or an ACT score ≥20 points   A. no importance  B. low importance  C. moderate importance  D. high importance  E. very high importance |
| 1. To decrease the number of asthma exacerbations requiring OCS by 50%   A. no importance  B. low importance  C. moderate importance  D. high importance  E. very high importance | 1. To have no asthma exacerbation requiring OCS   A. no importance  B. low importance  C. moderate importance  D. high importance  E. very high importance |
| 1. To improve the FEV1 by 10%   A. no importance  B. low importance  C. moderate importance  D. high importance  E. very high importance | 1. To improve the FEV1 by 12% and 200 mL   A. no importance  B. low importance  C. moderate importance  D. high importance  E. very high importance |
| 1. To reduce daily OCS dose by 50%   A. no importance  B. low importance  C. moderate importance  D. high importance  E. very high importance | 1. To achieve complete withdrawal of daily OCS   A. no importance  B. low importance  C. moderate importance  D. high importance  E. very high importance |
| 1. To have no side-effects   A. no importance  B. low importance  C. moderate importance  D. high importance  E. very high importance | 1. To have minimal side-effects   A. no importance  B. low importance  C. moderate importance  D. high importance  E. very high importance |

**Appendice**. Survey questionnaire

ACQ : Asthma Control Questionnaire ; ACT : Asthma Control Test ; OCS : oral corticosteroids ; FEV1 : forced expiratory volume in 1 second

Table 1. Characteristics of subjects involved in the survey

|  |  |
| --- | --- |
| **Parameter** (N=132) | **Value** |
| **Age,** mean ± standard deviation (years) | 55 ± 11 |
| **Gender,** no (%) male | 84 (64) |
| **Speciality,** no (%)  Pulmonologist  Allergologist  Internal Medicine specialist  Pediatric specialist  Public Health specialist | 70 (53)  42 (32)  9 (7)  9 (7)  2 (2) |
| **Country**, no (%)  France  Greece  Argentina  Italy  Mexico  Brazil  Romania  Bulgaria, Columbia, Spain  Ireland, Thailand  Afghanistan, Albania, Bangladesh, Hungary, Poland, Taiwan, United States  Algeria, Australia, Canada, Chile, Honduras, Japan, Panama, Paraguay, Peru, Singapore, Turkey, United Kingdom | 19 (14)  17 (13)  16 (12)  13 (10)  11 (8)  7 (5)  5 (4)  4 (3)  3 (2)  2 (2)  1 (1) |
| **Involved in the scientific dissemination of results**, no (%) | 64 (48) |

Table 2: Distribution of answers by items

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Item** | **\*A. No importance**  N (%) | **B. Low importance**  N (%) | **C. Moderate importance**  N (%) | **D. High importance**  N (%) | **E. Very high importance**  N (%) | **Mean ± SD** | **Median**  **[0 ; 10]** | **P-value** |
| 1. | 5 (4) | 15 (11) | 42 (32) | 45 (34) | 25 (19) | 7.1 ± 2.2 | 8 | **0.005** |
| 2. | 3 (2) | 6 (5) | 30 (23) | 56 (42) | 37 (28) | 7.8 ± 1.9 | 8 |
| 3. | 1 (1) | 2 (2) | 13 (10) | 57 (43) | 59 (45) | 8.6 ± 1.5 | 8 | 0.079 |
| 4. | 2 (2) | 2 (2) | 12 (9) | 41 (31) | 75 (57) | 8.9 ± 1.7 | 10 |
| 5. | 3 (2) | 25 (19) | 68 (52) | 29 (22) | 7 (5) | 6.2 ± 1.7 | 6 | 0.549 |
| 6. | 7 (5) | 26 (20) | 39 (30) | 46 (35) | 14 (11) | 6.3 ± 2.4 | 6 |
| 7. | 3 (2) | 2 (2) | 14 (11) | 53 (40) | 60 (45) | 8.5 ± 1.8 | 8 | **0.048** |
| 8. | 2 (2) | 6 (5) | 4 (3) | 30 (23) | 90 (68) | 9.0 ± 2.0 | 10 |
| 9. | 4 (3) | 5 (4) | 22 (17) | 52 (39) | 49 (37) | 8.1 ± 2.0 | 8 | 0.756 |
| 10. | 2 (2) | 12 (9) | 17 (13) | 54 (41) | 47 (36) | 8.0 ± 2.0 | 8 |

SD : standard deviation ; \*Scoring of answers : A = 2 points ; B = 4 points ; C = 6 points ; D=8 points ; E=10 points

**Figures legends**

**Figure 1 :** Distribution of the answers for the different items of the questionnaire

A : Q1&2 ; B : Q3&4 ; C : Q5&6 ; D : Q7&8 ; E : Q9&10

**Figure 2 :** Top 10 ranking according the answers

A : very high & high importance ; B : very high importance

**Figure 3** : Global Asthma Association criteria for evaluation of biological therapies efficacy in asthma

**Figure 4** : Spearman’s correlations of data