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Anti-interleukin 5 therapies failure criteria in severe asthma: a Delphi-consensus study

Laura Mattei¹, Carey M. Suehs, Khuder Alagha, Arnaud Bourdin, Christophe Brousse, Jeremy Charriot, Gilles Devouassoux, Stephanie Fry, Laurent Guilleminault, Marion Gouitaa, Camille Taille, Pascal Chanez and Laurie Pahus; on behalf of the CRISALIS network

Abstract

Background: Current practices for assessing response to anti-interleukin 5/R treatment in severe asthma patients are heterogeneous. The objective of this study was to achieve an expert consensus defining failure criteria for anti-interleukin 5/R treatment in severe asthma patients.

Methods: Experts were invited to a 5-round Delphi exercise if they were pulmonologists managing ≥ 30 patients at a nationally recognized severe asthma expert centre. Following two rounds of statement-generating brainstorming, the expert panel ranked each statement according to a 5-point Likert-type scale during three additional rounds. Positive consensus was considered achieved when $\geq 80\%$ of experts agreed with a statement with $>50\%$ strong agreement and $<15\%$ disagreement.

Results: Twenty experts participated in the study. All experts agreed that predefined treatment goals defining effectiveness should be personalized during shared decision making via a patient contract. Treatment failure was defined as (1) absence of a reduction in exacerbation rates by $\geq 25\%$ or (2) absence of a reduction in oral corticosteroid therapy by $\geq 25\%$ of the initial dosage or (3) occurrence of emergency room visits or hospitalizations after 6 months of treatment. Treatment failure should result in discontinuation. For partial responders, treatment discontinuation was not recommended unless an alternative from another therapeutic class exists and should be discussed in a multidisciplinary consultation.

Conclusion: The present study provides objective criteria for anti IL5 or IL5R failure in severe asthma and suggests consensus based guidelines for prescription, evaluation and discontinuation decision-making.

Keywords: anti-interleukin 5, anti-interleukin 5 receptor, failure, severe asthma

Introduction

Severe asthma management is a considerable burden for patients and a challenge for health-care professionals. It is responsible for significant health costs related to asthma treatment, comorbidities, hospitalizations and sick days.¹ Significant side effects are associated with certain severe asthma treatments, in particular oral corticosteroids (OCS). The latter are nonselective and associated with considerable multiorgan toxic effects and broad immunosuppression.² Strategies that minimize the need for corticosteroids have thus become a priority in severe asthma management.^{3,4}

Prior to 2016, patients with a severe allergic asthma phenotype only had access to omalizumab⁵ in terms of biologics. In 2016, 2018 and 2019, three other monoclonal antibodies with OCS-sparing potential were approved in France for high-T2 severe asthma patients: mepolizumab (an anti-IL-5 monoclonal antibody), benralizumab (an interleukin (IL)-5 receptor monoclonal antibody) and dupilumab (a monoclonal antibody that inhibits IL-4R and IL-13 binding to their receptor⁶⁻⁸), respectively. The responses to these treatments among severe asthma patients can be quite variable, ranging from complete

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remission of asthma, passing through a gradient of categories of partial responses, and ending at absolute failure.

Despite several years of availability, recommendations for cut-off points that would characterize treatment failure or partial response to anti IL-5/R mAb (benralizumab or mepolizumab) currently do not exist. Recently Perez de Llano and colleagues have developed a linear 100 points scale to quantify response to asthma biotherapies which may help weighting partial response but do not suggest failure cut-point to date.⁹ The practices for assessing therapeutic response and failure remain therefore highly heterogeneous. The identification of patients who do not adequately respond to a given mAb treatment represent nevertheless an important issue for prescribers. It is necessary to guide them by establishing a precise framework for determining when to stop this therapy in order to avoid exposing patients to ineffective, expensive treatment and to seek alternatives (for example, the more recent anti-IL4R/IL13R pathway) as soon as possible.

The objective of this study is therefore to provide a consensus defining failure criteria for anti-IL5 or IL5R treatment in severe asthma patients along with associated assessment thresholds to homogenize practice and stopping rules.

Methods

Study design

Expert opinions concerning anti-IL5 or IL5R treatment failure criteria were surveyed via a 5-step modified Delphi protocol (<https://osf.io/j83sf/>) from 11 March 2020 to 14 July 2020. The process consists in three phases: (1) the selection of relevant experts, (2) two brainstorming questionnaires during which the previously selected experts generated statements and (3) three ranking questionnaires during which the same experts assigned a five-level Likert-type value to each statement. Feedback from each questionnaire round was returned to the expert panel before proceeding with the next round.

Online survey software (SurveyMonkey; www.surveymonkey.com) was used to generate and manage the questionnaires while preserving expert anonymity and thus averting peer-pressure effects.¹⁰

Expert recruitment

All pulmonologists from the 12 French national severe asthma expert centres were invited by email to take part in the survey. Expert centres are defined as those affiliated with the national French CRISALIS network (Clinical Research Initiative for Severe Asthma).¹¹ Physicians from these sites were considered experts when responsible for the care and monitoring of at least 30 severe asthmatics.

Expert demographics

As part of the first questionnaire, participants were asked to provide demographic information, including gender and number of years of practice. Their level of expertise/activity was characterized by the number of severe asthmatic patients monitored, treated with biologics, prescribed anti-IL5 drugs, number of anti-IL5 prescriptions stopped for lack of efficacy or adverse reactions.

Brainstorming questionnaires and literature review

To launch the brainstorming process, the first questionnaire included open-ended questions to generate an initial list of raw statements relating to six categories: (1) predefined treatment goals when starting treatment, (2) cut-off points for evaluation, (3) the definition of treatment failure, (4) the notion of partial response along with the (5) management of patients in case of failure or (6) adverse effects. The results from the first round of brainstorming (B1) were grouped by theme and used to create a nonredundant, representative list of criteria which were then fed-back to all B1 participants.

While waiting on the B1 results, the related scientific literature was reviewed for already-published criteria. The point of our study is to precisely define failure criteria because the current medical literature lacks such a definition. Thus, the literature review was focused on response criteria used in clinical trials evaluating anti IL5 or IL5R drugs. This review was based on the following search criteria on clinicaltrials.gov: Severe Asthma, Mepolizumab, Benralizumab, Reslizumab. Based on the latter trials, a list of used efficacy criteria was created and sent to experts before the second brainstorming.

The feed-back from B1 along with the literature review was supposed to potentially inspire further

criteria, which were collected in the brainstorming 2 (B2) phase of the project. The answers to the second brainstorming were edited as for the first and then provided to all participants. At the end of B2, the statements provided by experts were categorized and filtered to avoid duplication and generate the final list of statements for the ranking phase of the process.

Item-rating questionnaire: ranking rounds

Following the brainstorming process, the final list of statements was individually presented via successive item-rating questionnaires to participants for ranking. Items were presented if initially suggested or considered as major criteria by at least 1/3 of the experts. A 5-point Likert-type scale was used to rank each item from “strongly disagree” to “strongly agree”. At the end of each round, results were fed back to participants. Serial ranking questionnaires continue with the same statements until stopping rules are met (consensus achieved at any round or consensus not achieved after three rounds of ranking). Once consensus was met for a given statement, the latter was not presented at the next round.

Consensus definition

Each ranking round results were considered relevant if 50% of centre participated. Consensus thresholds were established in an a priori fashion before the start of the study (<https://osf.io/j83sf/>). Positive consensus is considered achieved when $\geq 80\%$ of experts agreed with a statement with $> 50\%$ strong agreement and $< 15\%$ disagreement. Negative consensus is defined when $\geq 50\%$ indicated a disagreement. In any other case, the statement is considered as controversial.

Results

Experts

Of the 35 experts invited to participate in this Delphi study, 20 experts completed at least 1 of the 5 survey rounds. Of the 15 experts who took part in the first round of ranking, 10 experts completed all 3 rounds. These data are summarized in the study flowchart (Figure 1).

The demographics data and expertise of the panel are provided in Table 1. The experts had a median of 19 years of experience, with a median of 64

patients treated with anti-IL5 or IL5R each, with 19% stopping for ineffectiveness.

Ranking results

Ranking results for all three rounds are provided in Table 2. Anti-IL5 or IL5R response items submitted to the experts for ranking are those considered as major criteria during the brainstorming process (Figure 2).

Regarding predefined treatment objectives, the experts agreed that it is always necessary to establish a goals contract with the patient initiating anti-IL5 or IL5R treatment. The contract should be personalized for each patient, specify the initial assessment timeframe, be sent to all of the patient’s referring physicians and reviewed at 6 months. All of these goal-related proposals reached consensus in the first round.

The brainstorming and literature reviews provided several criteria that can be used to evaluate the therapeutic response to anti-IL5 or IL5R treatments. Lack of improvement in asthma control (daily symptoms/ control questionnaires) and lack of improvement in quality of life did not reach consensus as major decision criteria at the end of the ranking process and are thus considered minor criteria. The following reached consensus as major treatment failure criteria: (1) reduction in exacerbation rate of less than 25%, (2) reduction of oral corticosteroid therapy of less than 25% and (3) absence of reduction in emergency room visits, conventional hospitalizations or intensive care (no consensus was reached on a threshold for the latter criteria). The expert panel also agreed that when failure is established, the treatment can be stopped by any pulmonologist after consulting the prescriber. The latter applies even if the patient indicates that he or she is satisfied with the treatment.

When the level of response based on major criteria is only partial, experts indicated that the responses on minor criteria should be considered to assist decision making. The decision to stop treatment in this case also relies on available alternatives. Thus, stopping treatment for a partial response to major criteria is only recommended if an alternative from another pharmaceutical class exists, indicating a clear preference for switching rather than stopping. The consensus also supports that this decision should be approved by a multidisciplinary panel.

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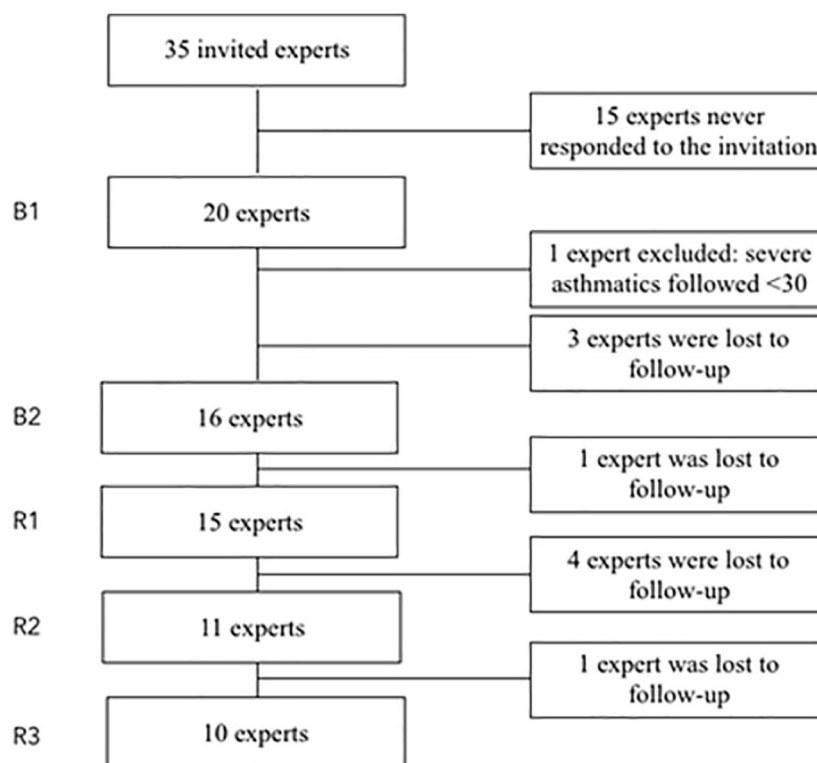


Figure 1. The study flowchart. B1/B2: Brainstorming rounds 1 or 2–R1/R2/R3: Ranking rounds 1, 2 or 3.

Table 1. Demographic data and characterization of the expert panel experience.

Variable	Percentage or median [IQR]
Gender, female (%)	40%
Average number of years of experience [min-max]	19 [4–40]
Average number of severe asthma patients followed [min-max]	185 [30–500]
Average number of severe asthma patients treated by bioterapy [min-max]	105 [15–360]
Average number of severe asthma patients treated or having been treated with anti-IL5 / R [min-max]	64 [13–300]
Reported percentage of patients for whom anti-IL5 / R treatment was stopped for ineffectiveness [min-max]	19% [3–38%]
Reported percentage of patients for whom anti-IL5 / R treatment was stopped for adverse event [min-max]	4% [0–13%]
IQR, interquartile range.	

Finally, if a serious treatment-related adverse event occurs, treatment can be stopped by any physician. However, no consensus was met in the event of a mild or moderate adverse event (Table 2).

Discussion

The main result of this study is the formulation of an expert consensus definition for anti-IL5 or IL5R treatment failure. The latter is tripartite and

Table 2. Results of the three ranking rounds.

Statements	Round	Number of experts	% Strongly agree	% Agree	% Neutral	% Disagree	% Strongly disagree	Consensus
Predefined treatment goals must always be set when initiating anti-IL5 treatment.	1	15	93	7	0	0	0	Positive
A goals contract is personalized for each patient.	1	15	80	20	0	0	0	Positive
The goals contract specifies the cut-off point for the initial assessment.	1	15	87	13	0	0	0	Positive
The goals contract must be specified in a report sent to the patient's referring physician(s).	1	15	73	13	13	0	0	Positive
Decrease in the annual rate of exacerbation is a major criterion.	1	15	93	7	0	0	0	Positive
Treatment fails if the reduction in the rate of exacerbation is less than								
25%	1	15	73	20	0	7	0	Positive
50%	1	15	27	40	7	27	0	Controversial
75%	1	15	7	7	13	40	35	Negative
100%	1	14	0	7	0	14	79	Negative
Not applicable, failure is not measured on this criterion	1	10	0	0	0	40	60	Negative
Reduction in the daily dose of oral corticosteroids is a major criterion.	1	15	93	7	0	0	0	Positive
Treatment fails if the reduction in the dosage of oral corticosteroids is less than:								
25%	1	15	53	40	7	0	0	Positive
50%	1	15	20	47	13	20	0	Controversial
75%	1	15	7	7	20	53	13	Negative
100%	1	15	7	0	7	13	73	Negative
Not applicable, failure is not measured on this criterion	1	10	0	0	0	40	60	Negative
Decrease in emergency room visits is a major criterion.	1	15	40	40	13	7	0	Controversial
Treatment fails if the decrease in emergency room visits is less than								
25%	2	11	55	27	18	0	0	Positive
Treatment fails if the decrease in emergency room visits is less than								
25%	1	13	62	15	15	8	0	Controversial
50%	1	13	15	46	23	15	0	Controversial
75%	1	13	15	8	23	31	15	Controversial
100%	1	13	23	0	15	0	46	Controversial

(Continued)

Table 2. (Continued)

Statements	Round	Number of experts	% Strongly agree	% Agree	% Neutral	% Disagree	% Strongly disagree	Consensus
Not applicable, failure is not measured on this criterion	1	11	9	18	9	27	27	Negative
25%	2	9	56	0	11	0	22	Controversial
50%	2	11	9	36	27	9	9	Controversial
75%	2	9	22	0	0	22	44	Negative
100%	2	9	22	0	0	11	56	Negative
Not applicable, failure is not measured on this criterion	2	-	-	-	-	-	-	NA
25%	3	9	22	0	11	11	33	Controversial
50%	3	10	10	30	20	0	20	Controversial
75%	3	-	-	-	-	-	--	NA
100%	3	-	-	-	-	-	-	NA
Not applicable, failure is not measured on this criterion	3	-	-	-	-	-	-	NA
Reduction in conventional hospitalizations is a major criterion.	1	15	67	20	13	0	0	Positive
Treatment fails if the reduction in conventional hospitalizations is less than								
25%	1	14	43	29	14	7	7	Controversial
50%	1	14	14	43	14	21	7	Controversial
75%	1	14	14	14	7	43	21	Negative
100%	1	14	21	7	14	0	57	Negative
Not applicable, failure is not measured on this criterion	1	11	0	18	9	27	45	Negative
25%	2	9	44	11	11	11	22	Controversial
50%	2	11	9	46	9	18	18	Controversial
75%	2	-	-	-	-	-	-	NA
100%	2	-	-	-	-	-	-	NA
Not applicable, failure is not measured on this criterion	2	-	-	-	-	-	-	NA
25%	3	9	33	11	0	33	22	Controversial
50%	3	10	20	10	40	20	10	Controversial

(Continued)

Table 2. (Continued)

Statements	Round	Number of experts	% Strongly agree	% Agree	% Neutral	% Disagree	% Strongly disagree	Consensus
75%	3	-	-	-	-	-	-	NA
100%	3	-	-	-	-	-	-	NA
Not applicable, failure is not measured on this criterion	3	-	-	-	-	-	-	NA
Reduction in intensive care hospitalizations is a major criterion.	1	15	80	13	7	0	0	Positive
Treatment fails if the reduction in intensive care hospitalizations is less than								
25%	1	14	43	36	0	14	7	Controversial
50%	1	14	36	14	7	36	7	Controversial
75%	1	14	21	21	0	29	29	Negative
100%	1	14	29	7	0	0	64	Negative
Not applicable, failure is not measured on this criterion	1	8	0	13	25	25	38	Negative
25%	2	10	50	20	0	0	30	Controversial
50%	2	10	40	20	0	20	20	Controversial
75%	2	-	-	-	-	-	-	NA
100%	2	-	-	-	-	-	-	NA
Not applicable, failure is not measured on this criterion	2	-	-	-	-	-	-	NA
25%	3	9	22	11	0	33	33	Negative
50%	3	10	30	10	20	10	30	Controversial
75%	3	-	-	-	-	-	-	NA
100%	3	-	-	-	-	-	-	NA
Not applicable, failure is not measured on this criterion	3	-	-	-	-	-	-	NA
Improving asthma control is a major criterion.	1	15	47	53	0	0	0	Controversial
	2	11	63	9	9	18	0	Controversial
	3	10	50	20	0	30	0	Controversial
Treatment fails if asthma								
Is uncontrolled	1	15	60	20	20	0	0	Controversial
Is partially controlled	1	15	13	27	27	27	7	Controversial

(Continued)

Table 2. (Continued)

Statements	Round	Number of experts	% Strongly agree	% Agree	% Neutral	% Disagree	% Strongly disagree	Consensus
Not applicable, failure is not measured on this criterion	1	10	0	10	20	30	40	Negative
Is uncontrolled	2	9	56	44	0	0	0	Controversial
Is partially controlled	2	9	22	11	56	0	11	Controversial
Not applicable, failure is not measured on this criterion	2	-	-	-	-	-	-	NA
Is uncontrolled	3	9	56	11	11	11	11	Controversial
Is partially controlled	3	9	11	44	11	22	11	Controversial
Not applicable, failure is not measured on this criterion	3	-	-	-	-	-	-	NA
Improving quality of life is a major criterion.	1	15	13	53	20	13	0	Controversial
	2	11	18	45	18	18	0	Controversial
	3	10	30	50	0	10	10	Controversial
Treatment fails if the quality of life:								
Is insufficient according to the patient	1	15	13	33	20	27	7	Controversial
Is insufficient according to a validated quality-of-life questionnaire	1	15	0	53	20	27	0	Controversial
Not applicable, failure is not measured on this criterion	1	11	0	27	9	27	36	Negative
Is insufficient according to the patient	2	11	22	44	11	0	22	Controversial
Is insufficient according to a validated quality of life questionnaire	2	11	20	40	20	0	20	Controversial
Not applicable, failure is not measured on this criterion	2	-	-	-	-	-	-	NA
Is insufficient according to the patient	3	10	20	50	10	10	10	Controversial
Is insufficient according to a validated quality of life questionnaire	3	10	10	50	10	10	20	Controversial
Not applicable, failure is not measured on this criterion	3	-	-	-	-	-	-	NA
Cut-off point for evaluation is 6 months.	1	15	53	33	13	0	0	Positive
In case of failure, treatment should be stopped.	1	15	40	40	13	7	0	Controversial
	2	11	72	27	0	0	0	Positive
In case of failure, the treatment can be stopped by a pulmonologist regardless of the place of practice, after consulting the prescriber.	1	15	20	33	0	40	7	Controversial
	2	11	55	27	0	0	9	Positive

(Continued)

Table 2. (Continued)

Statements	Round	Number of experts	% Strongly agree	% Agree	% Neutral	% Disagree	% Strongly disagree	Consensus
In case of a partial response to a major criterion, discontinuation of treatment should be discussed in a multidisciplinary consultation meeting.	1	15	27	40	13	20	0	Controversial
	2	11	18	63	0	9	9	Controversial
	3	10	50	30	10	10	0	Positive
In case of a partial response to a major criterion, the decision to stop treatment depends on the available alternatives.	1	15	53	47	0	0	0	Positive
In the event of a partial response to a major criterion, discontinuation of treatment is not recommended unless an alternative from another therapeutic class exists.	1	15	27	60	0	13	0	Controversial
	2	11	36	45	0	9	9	Controversial
	3	10	50	40	0	10	0	Positive
Response on minor criteria is used to adjust decision making in the event of a partial response.	1	15	20	73	0	7	0	Controversial
	2	11	45	55	0	0	0	Controversial
	3	10	60	40	0	0	0	Positive
Patient satisfaction is an essential prerequisite to continue treatment.	1	15	20	53	27	0	0	Controversial
	2	11	45	36	18	0	0	Controversial
	3	10	40	40	10	0	10	Controversial
In case of a mild or moderate adverse event, discontinuation of treatment should be discussed in a multidisciplinary consultation meeting after assessment of the benefit / risk ratio.	1	15	20	47	7	20	7	Controversial
	2	11	36	27	9	18	9	Controversial
	3	10	30	40	10	10	10	Controversial
In case of a serious treatment-related adverse event, treatment can be stopped by any physician.	1	15	73	13	0	7	7	Positive
NA, non applicable.								

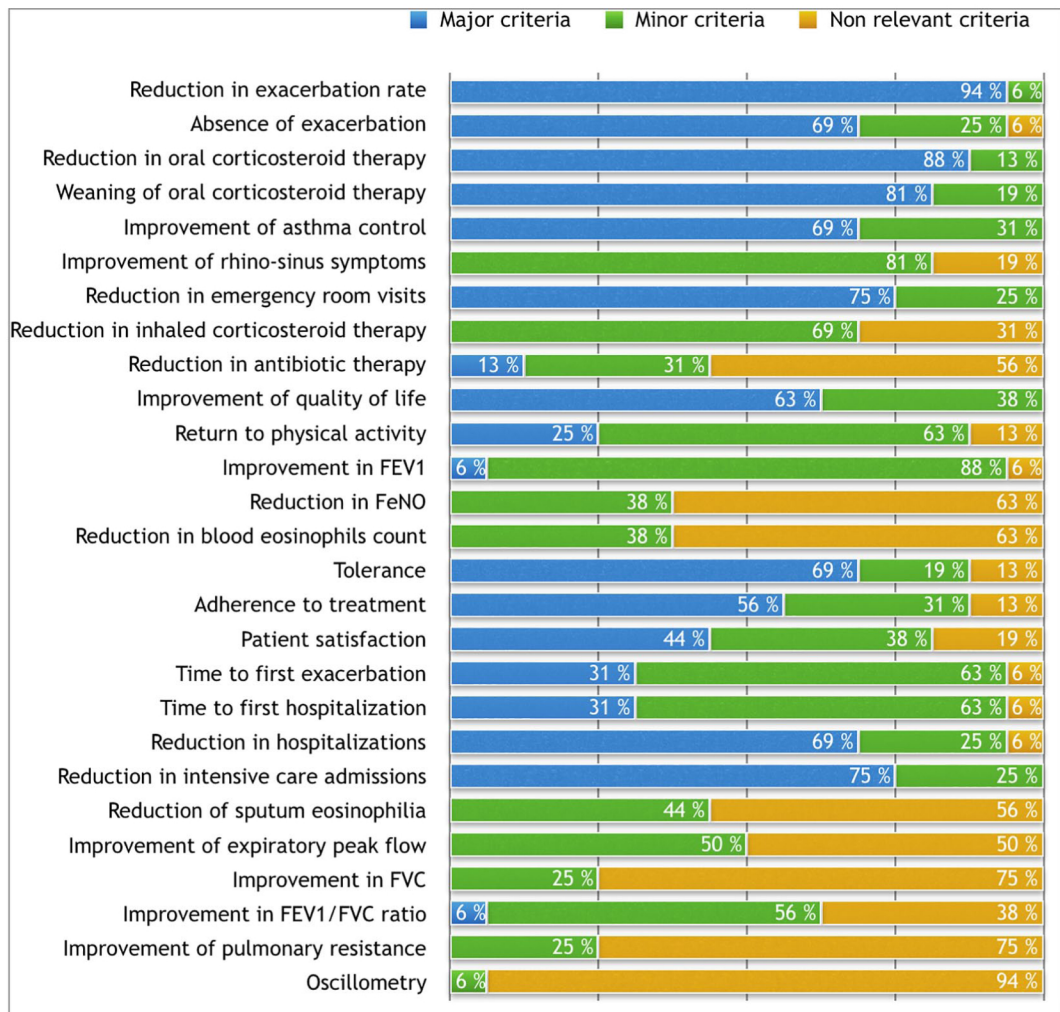


Figure 2. Categorization of anti-IL5 or IL5R response criteria by the panel ($n = 16$).

summarized as (1) absence of a reduction in exacerbation rates by at least 25% or (2) absence of a reduction in oral corticosteroid therapy by at least 25% of the initial dosage or (3) the occurrence of emergency room visits or hospitalizations (with or without intensive care) after 6 months of treatment. Treatment should be stopped when these criteria are met to avoid the unnecessary exposition of nonresponding patients.

To our knowledge, this is the first study characterizing anti-IL5 or IL5R treatment failure with objective consensus criteria. Acknowledging that experts recommendation are a weak level of evidence, this is the highest available to date to define anti IL5 or IL5R failure. In certain studies, thresholds have been proposed but set arbitrarily. Some considered inadequate response to anti-IL5

or IL5R when no reduction of exacerbation rate, no reduction of OCS dosage, no improvement in physical fitness, persistent severe obstruction in pulmonary function testing (PFT), inadequate treatment response according to patient, persistence of high T2 related biomarkers such as FeNO, persistence or even worsening of symptoms or persistence of uncontrolled comorbidities such as chronic rhinosinusitis or nasal polyps.^{12,13} Others considered sub-optimal response defined as failing to achieve either $\geq 50\%$ reduction in OCS dose, $\geq 50\%$ reduction in annualized exacerbation rate (AER), and an ongoing requirement of ≥ 7.5 mg prednisolone/day or an AER of ≥ 3 .¹⁴ The strength of our study is to base the notion of treatment failure on a robust definition established by consensus from an expert panel with appropriate knowledge of the issue. Common

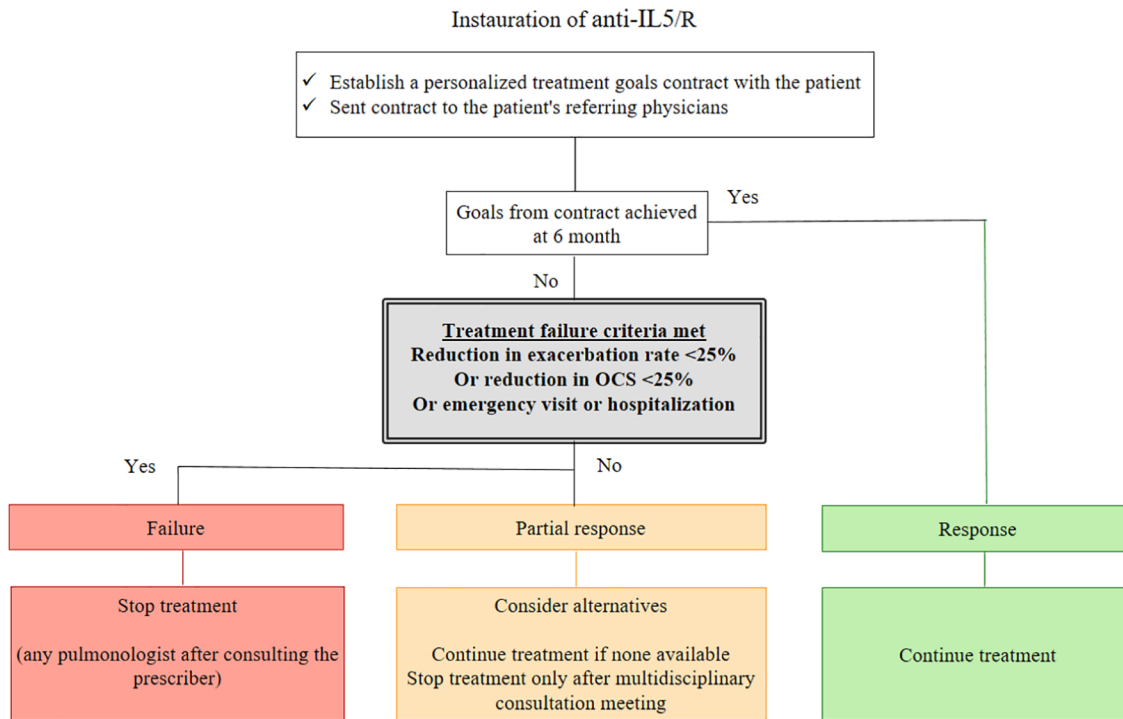


Figure 3. A summary of expert consensus recommendations based on the Delphi survey. OCS, oral corticosteroids.

criticism levelled at qualitative studies includes the subjectivity of a narrow panel.¹⁰ To minimize this bias, experts were selected via a nationally organized expert centre network to maximize relevance to the research question and the generalizability of the panel consensus to a wide distribution of experts.

In contrast to the across-the-board, treatment failure criteria, treatment efficacy goals were considered by the panel as a domain where case-by-case adaptation is required which is consistent with European Academy of Allergy and Clinical Immunology (EAACI) guidelines.¹⁵ Shared decision making is a model of the patient-physician relationship, defined as mutual sharing of information to build consensus about preferred treatment that culminates in an agreed action.^{16,17} Global Initiative for Asthma (GINA) guidelines state that effective asthma management requires the development of a partnership between the person with asthma and health care providers.¹⁸ Self-management education reduces asthma morbidity.¹⁹ There is emerging evidence that shared decision-making is associated with improved outcomes.²⁰ To date, the effectiveness of asthma treatment has

been evaluated according to global outcomes used in clinical trials which are not patient-specific.²¹⁻²³ In our study, all experts agreed that predefined treatment goals should be set with each patient, promoting shared decision making and personalized medicine. Thus, treatment efficacy should not be defined by pre-established thresholds homogenously applied to the entire asthma population.

Between adaptable, predefined, treatment efficacy goals and nonpersonalized treatment failure criteria, lies partial response. Treatment discontinuation was not recommended by the expert panel for partial responders unless an alternative from another therapeutic class exists and should be discussed in a multidisciplinary consultation meeting. In the absence of clear treatment failure, final decision making is shared with the patient. All consensus-based recommendations are summarized in Figure 3.

Our study is no exception to a common limitation of Delphi surveys:²⁴ the length of the process discouraged some experts, despite reminders and other procedures put in place to limit attrition. Moreover, the COVID-19 related situation at the

time of survey launching did not help participant retention. This possibility was acknowledged when designing this study and several experts from each site were invited to take part in order to optimize the chances that multiple sites were represented in the final consensus. Thus, a majority (67%) of the French expert centres initiating the process also completed it.

In conclusion, this study provides objective, easily applicable treatment failure criteria for anti-IL5 or IL5R biotherapies for the treatment of severe asthma. At the patient level, treatment stopping on validated criteria brings objectivity to therapeutic management. It will also help avoid unnecessary exposition of nonresponder patients to potential (though admittedly rare^{21,22}) adverse events and switching to a potentially more-efficient biotherapy when possible and needed. At the population level, such failure criteria will help identify and subsequently characterize nonresponders, an essential step prior to predicting treatment failure in identified phenotypes. In severe asthma, treatment sequences are often based on efficacy criteria and phenotypes overlap in terms of biotherapy options,²⁵ which can complicate how a physician chooses a first line of treatment. The diversity of available monoclonal antibodies and the overlap of their respective eligibility criteria necessitate the implementation of objective, stepwise, treatment strategies integrating treatment failure. The present work provides objective failure criteria for anti-IL5 or IL5R therapies. Further studies should determine if stopping criteria for other pharmacological classes (e.g. anti-IL4/13, anti-TSLP) are the same. The identification of non responders based these objective failure criteria may help implementing a “best treatment first” strategy when eligibility to several treatments exists.

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Author contributions

LM is the Guarantor. LM, CMS, and LP contributed to the conception and design. LM and LP contributed to analysis and interpretation. LM, LP, and PC contributed to redaction. LM, CMS, LP, KA, AB, CB, PC, JC, GD, SF, LG, MG, CT, and LP involved in correction.

Conflict of interest statement

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Data statement

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