Quantitative and qualitative methods of evaluating response to biologics in severe asthma patients: Results from a real-world study

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Clinical Implications

Proper identification of the response to biologics in asthma is an unmet need. In a real-world cohort, we evaluated the performance of the super-responder consensus definition and a quantitative tool showing that their concomitant use improves their identification.

Asthma is a complex major noncommunicable disease affecting around 333 million people worldwide, both children and adults.[1] New biological therapies for treating severe asthma have remarkably improved disease management. Notwithstanding, one remaining crucial problem is evaluating the response to these treatments. Therefore, adequate measurement of the response to biologics in a holistic manner that integrates clinical variables of interest and quality of life is needed, particularly in identifying super-responder patients (SR). Menzies-Gow et al[2] went more profound in the concept and proposed a consensus to evaluate remission.

Recently, 2 methods (qualitative and quantitative) for measuring the response to biologics in asthma were published. Following DELPHI consensus criteria, Upham et al[3] described a questionnaire to evaluate the achievement of clinical hallmarks, particularly trying to identify SRs. At least 2 major criteria (exacerbation elimination, major improvement in asthma control, or cessation of maintenance oral corticosteroids [OCS]) and 1 minor criterion (75% exacerbation reduction, Asthma Control Test [ACT] >19, or ≥500 mL improvement in forced expiratory volume in the first second [FEV_1]) should be fulfilled.

In addition, Pérez de Llano et al[4] proposed a quantitative score (the FEOS score [FEV_1, Exacerbations, OCS, Symptoms]) that allows clinicians to quantify responses in patients with severe asthma treated with biologics. It measures changes in 4 clinical parameters (FEV_1, severe exacerbations, OCS intake, symptoms) from baseline (before biologic initiation) to a follow-up time point. The maximal clinical improvement score (MI) varies according to the baseline disease burden. It is higher for those starting from a worse clinical situation: 100 for patients with ≥2 exacerbations and OCS use, 76 for patients with ≥2 exacerbations but no OCS use, 73 with no severe exacerbations but OCS use, and 49 with no exacerbations and no use of OCS. As there are no defined cutoffs for SRs in the FEOS score, we extrapolated the consensus framework for clinical asthma remission after treatment proposed by Menzies-Gow et al,[2] which is based on the same parameters evaluated in the FEOS score. Thus, defining SRs by no exacerbations and OCS intake, optimization and stabilization of lung function, and ACT ≥20, the SR FEOS minimum scores would be 98% for baseline category MI-100, 97% for MI-73 and MI-76, and 96% for MI-49.

Considering the evaluating tools described above, we decided to assess their performance in a real-world analysis of patients treated with different biologics.

Thirty-two patients with severe eosinophilic asthma treated with benralizumab, dupilumab, or mepolizumab were included in the study (Table I). Baseline conditions and improvement after treatment are shown. The following items were considered: OCS intake, annualized exacerbation rate, ACT, and FEV_1. Patients were categorized as SR and non-SR per Upham's criteria,[3] and the FEOS-weighted index was calculated.[4] Most patients received biologicals because of ≥2 exacerbations and/or OCS dependence (68.75%), although some were treated for poor lung function and/or low ACT (31.25%).

Following the SR consensus criteria, 59.4% of the patients were considered SR and 40.6% were non-SR. According to the clinical data, the SR group showed an average FEOS score of 96.8% ± 7.6%, and the non-SR group showed an average score of 80.3% ± 16.8%. This percentage of SRs in our series is high compared with similar real-world studies.[5,6] Two factors that could have influenced the ratio of SRs are the high mean levels of eosinophils and the presence of nasal polyposis (NP), which are the factors associated with better response to T2 biologics.[7] Notably, Kavanagh et al,[8] in a real-world study, found almost 40% of SRs and observed a statistically significantly higher rate of NP and higher mean eosinophil count in the SR group. Indeed, in our study, 75% of patients had NP, and the mean eosinophil count was 544 ± 497 cells/μL, which could have influenced the response rate.

At first sight, SRs presented higher FEOS scores, whereas non-SRs presented low FEOS scores. Nevertheless, when the 4 sets of MI of the FEOS index according to the baseline conditions were considered, we detected unexpected FEOS values in 21% of the patients in the SR group (low FEOS scores) and 24% in the non-SR group (higher FEOS scores), suggesting a possible interdependency between the FEOS and Upham's indexes. That was verified statistically by a significant association using Cohen's d coefficient[9] ($d = 1.25$, $P = .001$).

Thus, patient 4, who experienced severe exacerbations after treatment and scored 67% in the FEOS index, was classified as SR by Upham's criteria. In comparison, patient 29 showed a marked improvement in asthma control and scored 100% in the FEOS index, despite lying under Upham's criteria non-SR category because a patient without previous exacerbations and no OCS intake cannot qualify for SRs. These discrepancies are an example of the dependence of Upham's classification on baseline characteristics. To find possible disagreements in FEOS scores between Upham's non-SRs and SRs in all MI groups

TABLE I. Clinical characteristics of patients included in the study

			OCS		Severe exacerbations		ACT		FEV_1 (mL)		FEV_1 (%)		Score	
Patient ID	Diagnostics	Treatment	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	Upham's criteria	FEOS (%)
1	AA	Benralizumab	N	N	1	0	19	25	2760	3390	61	75	SR	97
2	AA	Benralizumab	N	N	2	0	19	25	2210	2880	75	107	SR	100
3	AA	Benralizumab	N	N	6	1	13	23	1530	1870	50	62	Non-SR	83
4	AA	Benralizumab	Y	N	2	2	10	22	1380	1610	34	40	SR	67
5	AA	Mepolizumab	N	N	2	1	10	23	1510	2520	61	112	Non-SR	86
6	NAA	Mepolizumab	Y	N	0	0	12	24	1750	2000	66	78	SR	98
7	AA; NSAID	Benralizumab	Y	N	0	0	8	24	2420	2393	65	64	SR	92
8	AA; NSAID; AD	Dupilumab	N	N	0	0	12	25	3620	3470	88	78	Non-SR	78
9	AA; NP	Benralizumab	N	N	4	0	15	25	2857	3962	75	104	SR	100
10	AA; NP	Benralizumab	N	N	3	0	12	22	2310	2910	67	91	SR	100
11	AA; NP	Dupilumab	Y	N	12	0	9	15	1840	3530	56	118	SR	96
12	AA; NP; AD	Dupilumab	Y	N	0	0	14	25	2250	3920	67	114	SR	100
13	NAA; NP	Benralizumab	Y	N	2	0	21	24	1900	2450	62	78	SR	98
14	NAA; NP	Benralizumab	N	N	1	2	8	22	1706	1896	57	63	Non-SR	47
15	NAA; NP	Benralizumab	Y	N	4	0	16	22	3570	3527	100	99	SR	100
16	NAA; NP	Benralizumab	Y	N	2	0	15	22	1860	2770	77	117	SR	100
17	NAA; NP	Benralizumab	Y	N	4	0	15	25	2095	3350	60	95	SR	100
18	NAA; NP	Mepolizumab	Y	N	0	0	10	21	2160	2440	123	141	SR	100
19	NAA; NP	Dupilumab	Y	N	12	0	8	25	1900	3470	58	105	SR	100
20	NAA; NP	Dupilumab	N	N	0	0	20	25	2220	2230	71	71	Non-SR	88
21	NAA; NP	Dupilumab	Y	Y	7	0	15	25	2670	2490	77	67	Non-SR	65
22	AERD	Benralizumab	Y	N	3	0	10	23	1780	3350	54	102	SR	100
23	AERD	Benralizumab	Y	N	4	0	8	23	1060	2460	28	65	SR	98
24	AERD	Benralizumab	N	N	6	2	9	23	1477	2130	66	96	Non-SR	86
25	AERD	Mepolizumab	Y	N	2	0	11	18	1130	1480	36	50	SR	94
26	AERD	Mepolizumab	N	N	6	1	12	24	2990	3150	84	89	Non-SR	86
27	AERD	Mepolizumab	Y	Y	0	0	15	17	2719	3230	88	109	Non-SR	56
28	AERD	Dupilumab	N	N	0	0	24	24	2760	3290	78	92	Non-SR	100
29	AERD	Dupilumab	N	N	0	0	14	24	4260	4780	109	113	Non-SR	100
30	AERD	Dupilumab	N	N	3	0	11	23	2780	3530	78	127	SR	100
31	AERD	Dupilumab	N	N	0	0	11	25	3310	3720	80	99	Non-SR	100
32	AERD	Dupilumab	N	N	0	0	8	20	2080	1930	78	67	Non-SR	69

Clinical data of patients were collected before starting treatment (PRE) and after 6 months of treatment (POST). Severe exacerbations were annualized to calculate the scores. *AA*, Allergic asthma; *ACT*, Asthma Control Test; *AD*, atopic dermatitis; *AERD*, aspirin-exacerbated respiratory disease; *FEOS%*, FEOS score; FEV_1, forced expiratory volume in 1 second; *N*, no oral corticosteroids intake; *NAA*, nonallergic asthma; *Non-SR*, non−super-responder; *NP*, nasal polyposis; *NSAID*, nonsteroidal anti-inflammatory drugs intolerance; *OCS*, oral corticosteroids; *SR*, super-responder; *Y*, oral corticosteroids intake.

(Table E1 and Figure E1, available in this article's Online Repository at www.jaci-inpractice.org), Student's *t*-test was used to assess statistical differences between any pair of independent groups ($n > 1$). Unexpectedly, we could not detect significant differences in the FEOS index between the non-SR group of the MI-49 category and the SR group in the MI-100 and MI-73 categories ($P > .05$), pointing to discrepancies among the Upham and FEOS methods when evaluating some patients who do not fulfill all Upham's criteria. That seems related to selection criteria, as MI-49 patients did not have exacerbations nor OCS use at baseline.

Thus, the differences observed in some patients might result from a classification based on excluding categories that, in addition, present redundancies among major and minor criteria, as observed in the SR definition proposed by Upham et al.[5] In contrast, the FEOS score provides a continuum of values, more accurately reflecting the heterogeneity of patients' response.

The accurate assessment of the response to the biological therapies for severe asthma is essential, not only in case of poor response to the treatments but also to identify an optimal response. We suggest that the correct classification of the patients could be implemented by calculating both indexes. When discrepancies appear, each case must be evaluated in detail, considering the individual clinical characteristic of this complex disease.

HUMAN STUDIES CONSENT

The Clinical Research Ethics Committee of the Institute for Biomedical Research of Salamanca (IBSAL) approved the study (PI 2020-02-433), and informed written consent was obtained from study subjects.

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This study has been funded by the projects PI20/00268 by the Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union; RD21/0002/0037, funded by Instituto de Salud Carlos III (ISCIII) and European Union -Next Generation EU, Mecanismo para la Recuperación y la Resiliencia (MRR); IMP/00009, funded by Instituto de Salud Carlos III (ISCIII) and European Regional Development Fund "A way to make Europe"; by the Grant PID2021-125117OB-I00 funded by MCIN/AEI/10.13039/501100011033 and by "ERDF A way of making Europe"; by the grant IES161P20 funded by Junta de Castilla y León and by "ERDF A way to make Europe"; and by Instituto de Salud Carlos III's Thematic Network of Cooperative Research in Health—RETICS (Red temática de investigación en salud Asma, Reacciones Adversas y Alérgicas, ARADyAL), grant number RD16/0006/0019, cofunded by the European Regional Development Fund (ERDF).

Conflicts of interest: In the last 3 years, I. Dávila has received payment for lectures, including service on speaker's bureaus, from Allergy Therapeutics, AstraZeneca, Chiesi, Diater, GSK, Leti, Novartis, and Sanofi; for a consultancy from Allergy Therapeutics, ALK-Abello, AstraZeneca, GSK, Merck, MSD, Novartis, and Sanofi; and grants for Thermofisher Diagnostics. J. Ramos-González has received payments for lectures from AstraZeneca, Chiesi, GSK, Novartis, Sanofi, Menarini, and Boehringer; and for a consultancy from AstraZeneca, GSK, Novartis, and Sanofi. M. Gil-Melcón has received payment for lectures from AstraZeneca, GSK, and Sanofi. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 30, 2022; revised October 24, 2022; accepted for publication November 4, 2022.
Available online November 22, 2022.

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2213-2198

https://doi.org/10.1016/j.jaip.2022.11.009

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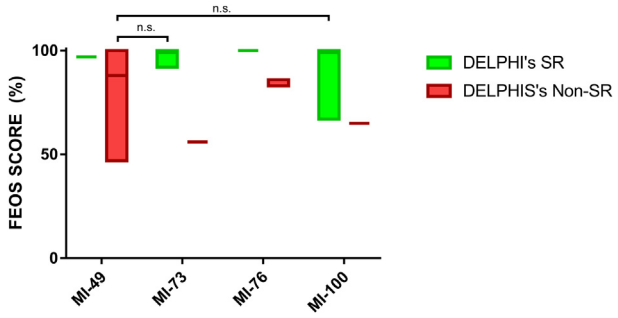

FIGURE E1. Distribution of the FEOS scores in the 4 groups comparing DELPHI's super-responders (SRs) and non-SRs using a *t*-test. Unexpected statistically nonsignificant (n.s.; $P > .05$) statistical results are shown. Data from MI-49 SR, MI-73 non-SR, and MI-100 non-SR were not compared as they included only 1 patient. *FEOS*, FEV_1, Exacerbations, OCS, Symptoms; *MI*, maximal clinical improvement score.

TABLE E1. Patient distribution according to the maximal improvement baseline conditions of the FEOS classification

	Maximal improvement—FEOS							
	49		73		76		100	
DELPHI	Non-SR	SR	Non-SR	SR	Non-SR	SR	Non-SR	SR
N	7	1	1	4	4	4	1	10
Mean ± SD	83.1 ± 20.0	97.0	56	97.5 ± 3.8	85.3 ± 1.5	100 ± 0	65	95.3 ± 10.2

FEOS, FEV_1, Exacerbations, OCS, Symptoms; *SD*, standard deviation; *SR*, super-responder.