Combination of Allergic Asthma Symptom and Medication Scores in Allergen Immunotherapy Trials: A Proposal

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Specific allergen immunotherapy (AIT) has been successfully used over 100 years to treat allergic rhinitis [1] and allergic asthma [2]. It is recognized as an effective modifier of the biological immune response [3]. The research field of AIT is continuously evolving and includes different allergen modifications, galenic presentations, adjuvants, and various routes and schedules of administration.

Randomized clinical trials must be conducted to demonstrate safety and efficacy and must follow the current guidelines [4]. For this purpose, the European Medicines Agency (EMA) released the “Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases” [5] stating that, in AIT trials, the primary endpoint has “to reflect both, symptom severity as well as the intake of rescue medication.” However, no validated method for the evaluation of the scores of asthma symptom and medication in a single combined score is available.

Therefore, there is a need for a method which combines asthma symptom score (SS) and medication score

(MS). The European Academy of Allergy and Clinical Immunology published a consensus related to the combination of symptom and MSs (CSMS) to be used in AIT trials for allergic rhinoconjunctivitis (RC) [4]. It is based on an equal weight of the total daily SS (dSS) and total daily MSs (dMSs). In this publication, the authors state as advantages the existence of a well-defined terminology of eye and nose symptoms, together with the 0–3 Likert scale symptom score which is accepted by the EMA and the Food and Drug Administration (FDA). The dSS is the sum of all individual symptoms divided by the number of symptoms, being the range of dSS from 0 to 3 (being 3 the maximum score). The difficulty of scoring medication was solved using a stepwise of the rescue medication, based on a slight modification of the Statement of the World Allergy Organization taskforce [6].

- Step 0: no use of medication. Scored as 0.
- Step 1: use of oral and/or topical (eyes and/or nose) non-sedative antihistamines (H1A). Scored as 1.
- Step 2: use of intranasal corticosteroids with/without H1A. Scored as 2.

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Fig. 1. Proposed stepwise and scoring for asthma medication. dMS, daily medication score; SABA, short acting beta agonist; ICS, inhaled corticosteroids; LTRA, leukotriene-receptor antagonists; LABA, long acting beta agonist.

Step	Medication	Score
Step 6	High-dose ICS + LABA + systemic corticosteroids with/without LTRA with/without SABA as needed	3.0
Step 5	High-dose ICS + LABA with/without LTRA with/without SABA as needed	2.5
Step 4	Medium-dose ICS + LABA with/without LTRA with/without SABA as needed	2.0
Step 3	Low-dose ICS + LABA or medium-dose ICS with/without LTRA with/without SABA as needed	1.5
Step 2	Low-dose ICS Alternative: LTRA with/without SABA as needed	1.0
Step 1	SABA as needed	0.5
Total daily medication score (dMS)		0–3

- Step 3: use of oral corticosteroids with/without intranasal corticosteroids, with/without H1A. Scored as 3. The dMS ranges from 0 to 3. The CSMS is the sum of dSS (range 0–3) and dMS (range 0–3). Therefore, the values of CSMS are in the range of 0–6.

However, no consensus exists related to the combination of SS and MS in AIT trials for allergic asthma. There are scales like Asthma Control Test (ACT) [7] or Asthma Control Questionnaire (ACQ) [7], but they do not evaluate the medication and symptoms in a combined way.

We propose that a similar model of CSMS in AIT trials for allergic RC could be used in AIT trials for allergic asthma. Related to asthma symptoms, there are 4 well-defined and accepted symptoms in asthma: cough, wheeze, shortness of breath, and chest tightness [8, 9], being the four-point Likert scale (0–3) used in several clinical trials for scoring these symptoms. The score is 0 for no symptoms, 1 for mild symptoms (minimal awareness and easy tolerated), 2 for moderate symptoms (definite awareness of symptom, i.e., bothersome but tolerable), and 3 for severe symptoms (symptoms which are hard to tolerate and cause interference with daily living and/or sleeping activities).

Each of the symptoms is scored from 0 to 3, considering the severity of each value. The final dSS of asthma would be the sum of all individual symptom scores divided by the number of symptoms, being the range of dSS from 0 to 3.

Related to medication, a stepwise treatment of asthma is described in GINA [9] and GEMA [8]. We propose a stepwise dMS for medication (Fig. 1), based on GINA and GEMA, to be used in clinical trials of AIT in asthma.

The proposed asthma CSMS is the sum of dSS (range 0–3) and dMS (range 0–3), being the values of CSMS in the range of 0–6 (sum of dSS and dMS). With this approach, the equal weight of the total dSS and total dMS can be achieved.

The use of this CSMS does not imply that this could substitute methods already used for the assessment of asthma control such scales like ACT [7] or Asthma Quality of Life Questionnaire (AQLQ) [10]. However, it could be a complement to evaluate the effect of AIT in asthma. In similarity with the statement of the unmet need of psychometric validation in the publication of the RC CSMS [4], this proposed asthma CSMS needs this validation too in clinical trials, which are already ongoing.

Statement of Ethics

Not applicable.

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Conflict of Interest Statement

All authors are employees of Inmunotek, S.L.

Author Contributions

R.C., A.G., G.J., and M.C. have made substantial contributions to the conception of this proposal. S.d.P., M.R., and M.L. have made contributions in review and draw.

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