



Patient-reported outcomes in asthma clinical trials

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Purpose of review

The review provides an overview of the results of asthma clinical trials published in peer review journals in the last 18 months that evaluated patient-reported outcomes (PROs).

Recent findings

In the last 10 years, health care moved toward a patient-centered approach, which includes patients' perspectives reflecting the impact of a disease and its treatment.

Summary

Surprisingly, among the almost 300 clinical trials published in the last one and a half year, PRO evaluation was performed in only 20 studies, and none of them held in a real-life setting. The effort of applying the scientific methods of PRO investigations in asthma clinical trials following a rigorous and systematic approach needs to be highly improved to allow better understanding of patient reported factors. Some recommendations are drawn particularly about PRO assessment in personalized medicine research. The ability of an individual PRO to evaluate choice of treatment and its effectiveness remains to be achieved.

Keywords

asthma, asthma control, health status, patient-reported outcomes, quality of life

INTRODUCTION

In the last decade, health care moved from a disease-centered approach, which emphasizes physiological indices of health, toward a patient-centered approach, which reflects the patient's viewpoint on the impact of a disease and its treatment. Furthermore, patient-reported outcomes (PROs), defined as 'any report coming from patients about a health condition and its treatment' [1], have gained increasing awareness and emphasis in clinical research. In addition, regulatory bodies have started to include the measurement of PROs as a step for the approval of new drugs and devices [2,3].

One of the major aims of asthma treatment is to improve the patient's health status that is influenced by functional, biological and subjective parameters. Therefore, an increasing number of clinical trials on asthma include PROs. Taking into account that the patient's perspective represents a crucial aspect of clinical research, the collection and management of data coming from such PROs should follow a rigorous approach. To provide an accurate account, specific guidelines and recommendations that lead to a correct PRO assessment are currently available [4,5].

OBJECTIVE

The review provides an overview of recent scientific publications of asthma clinical trials that include PROs as outcome measures.

METHODS

Studies were sought from PubMed archives. The following keywords were used: Asthma [AND] each PRO considered in the GA2LEN task force position paper on PROs and quality of life assessment [4]. Only clinical trials assessing health-related quality of life (HRQoL), health status, well being, satisfaction, adherence, illness perception, preferences, control, symptoms, work productivity by means of validated tools, published in peer review journal from January 2016 to June 2017, were considered.

RESULTS

Only 20 trials explored PROs using validated tools but, among PROs utilized, only health-related quality of life (HRQL), health status, control and symptoms were evaluated (Table 1). Fifteen studies explored the impact of an intervention on HRQoL,

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KEY POINTS

- The aim of asthma treatment is to improve patient's health in terms of functional, biological and subjective parameters.
- PROs must be evaluated by validated tools, and questionnaires selected should be suitable for the clinical setting under investigation and consider the concomitant comorbidities, specific symptoms pattern and specific functional aspects.
- Whenever available, a specific tool that assesses a single outcome (e.g. effect on sleep) should be used.
- The effort of applying scientific methods for PROs evaluation in asthma clinical trials should follow a rigorous and systematic approach to better understand patient-related factors influencing real-life management outcomes.

using Asthma Quality of Life Questionnaire (AQLQ) in 10, mini-AQLQ in four, Asthma Bother Profile (ABP) in one. The minimal clinical difference [minimal important difference (MID)] [26] was assessed in six trials, and, only in one case out 15, HRQL was the primary outcome. Asthma control was explored using the Asthma Control Test (ACT) in four trials and the Asthma Control Questionnaire (ACQ) in 19 trials. The latter has been used in the seven items form [including forced expiratory volume in 1 second (FEV1)] in seven trials, and in two studies, disease control was the primary outcome. The MID was considered in eight trials. Health status, explored using short form 36 health survey (SF-36), was included in two trials (both assessing the MID), whereas symptoms were assessed in two trials by means of the Asthma Symptoms Utility Index (ASUI), and in one trial as primary outcome using Wisconsin Upper Respiratory Symptom Survey (WURSS-21), for which the MID was evaluated. Due to the variety of investigated interventions, the abovementioned studies were presented grouped in trials investigating populations of asthma patients who presented different clinical patterns, different schedules of drugs, biologicals molecules and nonpharmacological treatments.

Patient-reported outcomes in trials evaluating patients with asthma in different clinical settings

In a retrospective analysis of a randomized placebo-controlled study (RCT) in patients with uncontrolled asthma despite the use of inhaled corticosteroid (ICS), Quezada *et al.* demonstrated a significant association between increased risk of

asthma exacerbation and lower asthma control (ACQ), higher symptoms (ASUI) and worse HRQoL (mini-AQLQ). Moreover, a significantly increased incidence of asthma exacerbations was reported after adjustment for age, sex, race and baseline FEV1 [6]. Other authors determined that PROs stability can vary according to patients' severity and control: the variability ranged from 13 (controlled patients) to 60% (uncontrolled patients) in mild asthma (non-ICS-treated), from 20 (controlled patients) to 65% (uncontrolled patients) in moderate asthma and from 21 (controlled patients) to 35% (uncontrolled patients) in severe asthma. AQLQ showed a greater stability over time compared with ACQ: the variability range was 18–26% in mild asthma, and lower in patients with moderate and severe asthma [7].

PROs were also evaluated in adult patients with or without insomnia. It was shown that participants with insomnia reported a worse asthma control. More than 75% of patients with insomnia were uncontrolled (ACT < 19), whereas not well controlled asthma was detected in only 50% of those without insomnia (chi square = 41.19, $P < 0.001$). Among the patients with uncontrolled asthma, those without insomnia had a better asthma control compared with those with insomnia (mean ACT score = 12.77 ± 4.01 and 15.12 ± 3.18 , respectively) ($t = 6.82$, $P < 0.001$). Furthermore, patients with insomnia showed significantly lower scores in AQLQ domains and total scores (thus, indicating worse HRQoL) [8].

Patient-reported outcomes in trials evaluating nonrespiratory and respiratory medications

Vitamin D supplementation did not reduce disease burden in asthma patients with vitamin D insufficiency, neither in terms of cold symptom occurrence and severity (assessed by WURSS-21 as a primary outcome) nor in asthma control (ACT) and quality of life (ABP) [9]. Similarly, three sequential doses of DAS181 10 mg (an inhaled antiviral with a unique mechanism of action) in not well controlled asthma adult patients did not improve health status (SF-36) nor level of control (ACQ-7). HRQoL scores (AQLQ) significantly improved from baseline, but the MID was not achieved [10].

A significant greater improvement in impulse oscillometry outcomes after chronic treatment with formoterol compared with salmeterol was demonstrated in one study with no significant difference in asthma control (ACQ-6) [11].

Improvement in PROs were shown using different treatment schedules in a secondary analysis of a

Table 1. Recent asthma clinical trials evaluating patient-reported outcomes

Reference	Trial intervention	Number of patients	Study duration	HRQoL	Health status	Control	Symptoms
Quezada <i>et al.</i> [6]	- Proton pump inhibitor (added to asthma controller therapy) - placebo (added to asthma controller therapy)	412	24 weeks	Mini-AQLQ		ACQ	Asthma Symptom Utility Index
Silkoff <i>et al.</i> [7]	Usual care	158 (no randomization)	12 months	AQLQ		ACQ7	
Luyster <i>et al.</i> [8]	No intervention (observational trial)	714	–	AQLQ		ACT	
Denlinger <i>et al.</i> [9]	- Cholecalciferol for 28 weeks (100000 IU once, then 4000 IU/day for 28 weeks) as add-on therapy in the background of a tapering ICS protocol - Placebo	2013	28 weeks	Asthma Bothers Profile		ACT ^a	Wisconsin Upper Respiratory Symptom Survey (WURSS-21) ^{a,b}
Colombo <i>et al.</i> [10 [†]]	- DAS181 10 mg on 3 consecutive days - Placebo on 3 consecutive days	11	6 weeks	AQLQ ^a	SF-36 ^a	ACQ7 ^a	
Manoharan <i>et al.</i> [11]	50 mg of dry powder inhaler salmeterol twice daily 2 mg of HFA-formoterol solution twice daily	17	1–2-week treatment 1–2-week washout period 1–2-week treatment			ACQ6	
Pilcher <i>et al.</i> [12]	- SMART regimen (200/6-μg budesonide/formoterol via MDI for maintenance (two actuations twice daily) and one actuation as required for symptom relief - Standard regimen (200/6-μg budesonide/formoterol (via MDI for maintenance (two actuations twice daily) and 100-μg salbutamol via MDI, 1–2 actuations as required for symptom relief	202	24 weeks			ACQ7	
Biermer <i>et al.</i> [13]	- Reslizumab 0.3 mg/kg - Reslizumab 3.0 mg/kg - Placebo	315	22–24 weeks	AQLQ ^a		ACQ 7 ^a ACQ-6 ^a ACQ-5 ^a	Asthma Symptom Utility Index
Corren <i>et al.</i> [14]	- Intravenous reslizumab 3.0 mg/kg - Placebo	496	16 weeks			ACQ7 ^a	
Bleeker <i>et al.</i> [15]	- Benralizumab 30 mg either every 4 weeks (add-on to standard treatment) - Benralizumab 30 mg either every 8 weeks (add-on to standard treatment) - Placebo (add-on to standard treatment)	1205 (including adolescents)	48 weeks	AQLQ		ACQ-6	
FitzGerald <i>et al.</i> [16]	- Benralizumab 30 mg either every 4 weeks (add-on to standard treatment) - Benralizumab 30 mg either every 8 weeks (add-on to standard treatment) - Placebo (add-on to standard treatment)	2505 (including adolescents)	60 weeks	AQLQ		ACQ6	

Table 1 (Continued)

Reference	Trial intervention	Number of patients	Study duration	HRQoL	Health status	Control	Symptoms
Harris <i>et al.</i> [17]	• Quilizumab 150 mg • Quilizumab 300 mg • Quilizumab 450 mg • Placebo	578	36 weeks	AQLQ		ACQ-5	
Kuna <i>et al.</i> [18]	STUDY 1 (withdrawal of all ICSs) • Supramaximal AZD1981 1000 mg twice daily • Placebo STUDY 2 (ICS) • AZD1981 50 mg/dose – one AZD1981 50 mg tablet and three placebo tablets bid • AZD1981 400 mg/dose – one AZD1981 250 mg tablet and three AZD1981 50 mg tablets bid • AZD1981 1000 mg/dose – four AZD1981 250 mg tablets bid • Placebo	113 368	4 weeks 4 weeks			ACQ5	
Virchow <i>et al.</i> [19]	• AIK HDM AIT 12 DU, oral lyophilisate for sublingual administration once daily • AIK HDM AIT 6 DU, oral lyophilisate for sublingual administration once daily • Placebo, oral lyophilisate for sublingual administration once daily	834	1 period: 5–7 weeks 2 period: 8–12 months 3 period: 6 months	AQLQ ^a		ACQ ^a	
Devillier <i>et al.</i> [20]	• House dust mite sublingual AIT • Placebo	484	12 months	AQLQ		ACQ-7	
Speck <i>et al.</i> [21]	• 6-week Breathe Michigan Program (self-management electronic program)	44	3 months	Mini-AQLQ ^a		ACT ^a	
Zairina <i>et al.</i> [22 [■]]	• Telehealth program • Usual care	72	6 months	Mini-AQLQ		ACQ-7 ^{a,b}	
Ma <i>et al.</i> [23 [■]]	• Dietitian-delivered behavioral intervention (DASH) • No intervention	90	6 months	Mini-AQLQ ^a		ACQ ^a	
Brinkhaus <i>et al.</i> [24 [■]]	• 3 months acupuncture treatment • 3 months no acupuncture	357 randomized (1088 nonrandomized)	6 months	AQLQ ^{a,b}	SF-36 ^a		
Salem <i>et al.</i> [25]	• <i>Nigella sativa</i> 1 mg (supplementation) • <i>Nigella sativa</i> 2 mg (supplementation) • Placebo (supplementation)	76	3 months			ACT	

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; DASH, Dietary Approaches to Stop Hypertension; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; MDI, metered dose inhaler; WURSS, Wisconsin Upper Respiratory Symptom Survey.

^aIndicates that the MID of questionnaire has been considered.

^bIndicates that the patient-reported outcome has been considered as primary outcome.

randomized study [27] which explored the effect of smoking status on the efficacy of a symbicort maintenance and reliever therapy (SMART) regimen compared with standard therapy in patients with high-risk asthma. The study results showed that clinical outcomes and PROs ran in parallel: the SMART group reported both fewer exacerbations and higher asthma control (ACQ7) ($P=0.023$) compared with standard [12] independent of smoking status.

Patient-reported outcomes in trials evaluating biologic therapies and allergen immunotherapy

Two different placebo controlled studies exploring the efficacy of reslizumab 3.0 mg/kg in patients with poorly controlled asthma demonstrated significant improvements in asthma control, quality of life and symptoms. In one study, Bjermer *et al.* [13] detected significant improvements in ACQ ($P=0.0014$), symptoms assessed by using ASUI ($P=0.016$) and AQLQ scores ($P=0.0241$). The MID was reached for AQLQ but not for ACQ. A modest but significant improvement of asthma control was also demonstrated by another study by Corren *et al.* [14] ($P=0.0457$).

The effect on asthma control with the use of benralizumab as add-on treatment to high-dose ICSs and long-acting β_2 -agonists was explored in two RCTs [15,16].

In the first study (SIROCCO), benralizumab treatment every 8 weeks significantly improved ACQ-6 ($P=0.0028$), whereas when administered every 4 weeks, the improvement was NS ($P=0.1107$). In the second study (CALIMA), a significant improvement in ACQ-6 scores was demonstrated both when the drug was administered every 4 (P value vs. placebo 0.0425) and 8 weeks (P value vs. placebo 0.0082). In both studies, AQLQ scores showed a significant improvement for patients treated with benralizumab every 8 weeks compared with placebo ($P=0.0036$ [15] and $P=0.0194$ [16]), whereas when administered every 4 weeks, it did not demonstrate a significant change ($P=0.0811$ [15] and $P=0.1194$ [16]).

On the other hand, the effects of quilizumab (an anti-M1-prime mAb that targets IgE-switched and IgE memory B cells) on PROs were NS: as a matter of fact, during the 36-week treatment, no significant differences were detected between quilizumab group and placebo in both HRQoL and asthma control, assessed by AQLQ and ACQ-5, respectively [17].

Kuna [18] performed two studies aimed at assessing the effects of the CRTH2 receptor antagonist, AZD1981 (with/without ICSs), on lung function and

asthma control. In the first trial, patients treated with AZD1981 1000 mg twice daily compared with placebo did not achieve a better control (ACQ-5), whereas in the second study, a significant reduction in ACQ-5 was demonstrated in all treatment groups compared with placebo: 50 mg ($P=0.047$), 400 mg ($P=0.042$) and 1000 mg ($P=0.014$).

In a placebo-controlled trial performed by Virchow [19] on adult patients not well controlled by ICS or combination treatment, 6 standardized quality (SQ) house dust mite (SQ-HDM) and 12 SQ-HDM tablets significantly reduced the risk of asthma exacerbations. Nevertheless, no effects on asthma control (ACQ) and quality of life (AQLQ) were demonstrated. Similar results were shown with the sublingual solution of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extracts. No significant differences compared with placebo were demonstrated in the proportion of patients lacking well controlled asthma (i.e. an ACQ score ≥ 1.5) or the change in the overall AQLQ [20].

Patient-reported outcomes in trials evaluating nonpharmacological interventions

Some studies evaluated the effect on asthma control and quality of life of specific interventions for targeted populations. For instance, Speck *et al.* [21] evaluated the feasibility of a self-management program in a group of young African-American adults at risk of unsatisfactory asthma outcomes; Zairina *et al.* [22[¶]] developed a supportive telehealth for pregnant women with uncontrolled asthma; and Ma *et al.* [23[¶]] involved 90 women with unsatisfactory asthma control in a healthy eating behavioral intervention. In all the above-mentioned studies, the interventions resulted in a significant improvement in both asthma control and quality of life.

PROs have been adopted also in studies that evaluate the effectiveness of unconventional treatments. For example, quality of life was the primary outcome in a study aimed to investigate the effectiveness of acupuncture added to routine care in patients with allergic asthma compared with ordinary treatment alone [24[¶]]. Acupuncture was associated with an improvement in the AQLQ score compared with the control group [difference acupuncture vs. control groups 0.7 (95% confidence interval 0.5–1.0)]. Health status, evaluated as secondary outcome, showed a significant improvement both in the physical component scale and in the mental component scale of the SF-36 [physical: 2.5 (1.0–4.0); mental 4.0 (2.1–6.0)].

Another study [25] reported a significant improvement in patients treated with *Nigella sativa* vs. baseline ($P<0.001$, <0.01).

CONCLUSION

Among the close to 300 asthma clinical trials published in the last 18 months, only 20 trials incorporated PROs evaluation. PROs evaluation in asthma clinical trials should follow a rigorous and systematic approach [1,28]. As of now, we lack consistent evidence that supports the use of any PROs validated tool over another for the assessment of different degrees of asthma. The choice of the tool should consider the clinical intervention or setting under investigation, the presence concomitant comorbidities (e.g. concomitant rhinitis or polyposis) [29,30], the specific symptom pattern (e.g. cough) [31–33] or the specific functional aspects [34–36], the length of the trial, the expected intervention effects, the recall period, the method of administration (self-administered and/or interview/telephone administered) and the format of administration (article or electronic version). Some questionnaires, despite being specific for the same disease, may not be interchangeable as they may analyze different aspects of the disease and therefore, may provide information on different dimensions of subjectivity. The MID is an important parameter for interpreting statistically significant PRO results and for determining the sample sizes when the PRO is used as the primary outcome. The MID, as well as responsiveness, may vary by population and context, and thus, one value cannot be considered valid for all studies [28,37,38].

As HRQoL assessment provides information on the impact of the disease but also of its intervention on patient's life, it is necessary to consider not only the functional and clinical parameters but also the ongoing treatment. This aspect seems to be of relevance in personalized medicine research in which several issues have to be considered. Although several validated tools for assessing HRQoL in asthma are currently available [39–55], AQLQ and its shortened version were the ones most often used in published research.

PROs are, up to now, rarely integrated in daily routine, albeit both common obstacle and possible solutions have been well described [56,57]. The need for PROs assessment in daily clinical practice has also been advocated [58–61]. The National Quality Forum [62] and the International Society for Quality of Life Research [63] have drawn up guidance for clinicians who want to properly assess the patient's perspective into practice. The insertion of PROs in the routine assessment may facilitate disease monitoring and management, enable patients to become more involved in the management of their disease, enhance the satisfaction with care and improve patient–physician communication [64–66].

Health Information Technology for Economic and Clinical Health introduced policy facilitators for incorporating PROs into practice and defined meaningful-use criteria for eligibility for federal incentives to increase the diffusion and use of electronic health records [67].

With the recent emphasis on personalized approach to treatment of asthma and the growth of targeted therapies for severe asthma, it is imperative that PROs be incorporated in clinical trials evaluating such interventions. For instance, many of the novel interventions are systematically administered, must be administered by a physician in the clinic/hospital, increase the contact with the medical staff/structure and minimize the self-management of the disease, and are perceived by patients as new drugs, and thus, their use is loaded with related expectations. All these dimensions should be explored to capture the patient's experience when such drugs are to be administered.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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