



Patient-reported outcomes and quality-of-life questionnaires in the assessment of rhinoconjunctivitis in childhood

Désirée Larenas-Linnemann^a and Oliver Pfaar^b

Purpose of review

Rhinoconjunctivitis, and especially allergic rhinoconjunctivitis (ARC) are increasing in prevalence, progressively affecting the well being of more and more adults and children. Clinical trials using allergen immunotherapy (AIT), the sole causal treatment of allergies, are being conducted, but discussions on optimal patient-related outcomes (PROs) are still ongoing.

Recent findings

Almost all publications discussing PROs relate to adults. The authors comment on the importance of broader PROs when assessing the results of AIT trials, as focusing on only nasal symptom improvement and medication reduction does not capture the full benefit of AIT. Such intervention also improves comorbid allergic diseases and general well being. In studies on rhinoconjunctivitis in children, using medical treatment or immunotherapy published between November 2012 – February 2014 nasal symptom (and medication) scores were primary outcomes in 18 of 20 trials. Only two trials applied quality-of-life questionnaires.

Summary

Clinical trials conducted in children with ARC should be interpreted with caution, as most currently used PROs give a restricted view, by not considering disease manifestations beyond nasal/ocular symptoms. To correctly estimate the full benefit of AIT in pediatric patients with ARC, broader PROs should be investigated, including disease control and quality of health.

Keywords

allergic rhinitis, conjunctivitis, immunotherapy, outcomes, rhinitis

INTRODUCTION

Allergic rhinitis and conjunctivitis have become increasingly prevalent over the recent decades. Data from the International Study on Allergy and Asthma in Childhood revealed an increase in the reported frequency of nasal symptoms in 6–7-year-old and 13–14-year-old children, reaching a worldwide mean of 8.5 and 14.6%, respectively [1]. This reflects the growing importance of this disease and as such, a need for clinical trials in children with rhinoconjunctivitis to help define the best treatment options. For an adequate evaluation, the medical community is in need of suitable tools to measure outcomes. Discussions on the best outcome measures in rhinoconjunctivitis trials have been ongoing for several years and the Global Allergy and Asthma European Network (GA2LEN) consensus report, published in 2010, provided recommendations for the evaluation of patient-related outcomes (PROs) in clinical trials for allergic diseases [2]. Since then, some new tools

have been presented, especially in the field of allergen immunotherapy (AIT) [3]. However, scores that have been developed and used in clinical trials on both sublingual and subcutaneous AIT are different to some extent [4^{*}]. Häfner *et al.* [5] evaluated and validated the Allergy-Control-SCORE in allergic adults: a 10-item symptom scoring system, which takes into account eye, nose, and bronchial symptoms, all scored on a 0–3-point scale. This system adds an adjusted daily medication score to

^aHospital Médica Sur, Mexico DF, Mexico and ^bDepartment of Otorhinolaryngology, Head and Neck Surgery, Center for Rhinology and Allergology, University Hospital Mannheim, Wiesbaden, Germany

Correspondence to Désirée Larenas-Linnemann, Puente de Piedra 150, Torre II-602, Colonia Toriello-Guerra, Delegación Tlalpan, 14050 México DF, México. Tel: +52 55 51712248; e-mail: marlar1@prodigy.net.mx

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KEY POINTS

- Almost all primary efficacy variables in trials investigating pediatric rhinoconjunctivitis are subjective patient-related outcomes.
- The mostly used tool is a symptom-medication scoring, sometimes including eye and bronchial symptoms.
- As children with ARC very often suffer from other comorbidities, an optimal patient-related outcome should include issues beyond the nose-eye.
- Respiratory health-related questionnaires are valid tools both in children and adolescents.
- It could be argued whether tools measuring control and/or disease-specific quality of life should be primary efficacy variables added to the medication score, especially in trials of pediatric ARC.
- Standardized measures of impairment and risk for children with allergic rhinitis are needed to permit better comparison between interventions.

the symptom score. Recently, the same group published a similar scoring system with a focus on rhinoconjunctival symptoms, investigated again, on adult allergic patients [6[¶]]. Another method has been reported as the Average Adjusted Symptom Score (AdSS) by Grouin *et al.* [7,8].

A broad discussion on which measures are 'ideally' useful outcome measures in both adult and pediatric patients has been addressed by different groups such as an expert group of the European Academy of Allergy and Clinical Immunology (EAACI) for AIT trials (<http://www.eaaci.org/component/content/article/2293.html>). However, only a few papers are starting to focus on the pediatric age group with regard to this particular question. The authors consider there are several issues that have to be taken into account when defining the best suitable outcome measure in the pediatric population (see Table 1).

Table 1. Selection of patient-related outcomes for trials in patients with rhinoconjunctivitis: issues to be taken into account

The phenotype of rhinoconjunctivitis being treated:

Allergic, immunoglobulin E-mediated rhinoconjunctivitis versus nonallergic rhinoconjunctivitis.

Adult versus pediatric rhinoconjunctivitis.

The nature of the intervention being evaluated

Symptoms beyond rhinoconjunctivitis:

Comorbidities and health-related quality of life

In this article, we review each of the variables from Table 1 in further detail. We discuss how each item impacts on the selection of outcome measures. The second part of the article discusses different outcome measures. The third part of this writing is a review of some studies published over the past 16 months in children with rhinitis and/or conjunctivitis, with special focus on the outcome measures selected and the results obtained.

The phenotype of rhinoconjunctivitis being treated

In children, the two most prevalent types of rhinoconjunctivitis are infectious and allergic, as non-allergic chronic rhinitis is rare in children. Thus, this analysis focuses on allergic rhinoconjunctivitis (ARC), the most frequent chronic form.

Allergic, immunoglobulin E-mediated rhinitis versus nonallergic rhinitis

Many children with ARC simultaneously suffer from other allergic diseases [9], especially allergic asthma or atopic dermatitis [10]. Pharmacotherapy given systemically (e.g. antihistamines or antileucotrienes) might improve not only nasal symptoms, but also symptoms of the comorbid allergic conditions. Thus, measuring only nasal symptom and medication scores might not record the complete benefit of the treatment. This holds true for interventions directed against the underlying cause, such as AIT. The scoring systems that evaluate the impact of such intervention should take into account symptoms of all organ systems involved (European Medicines Agency guideline 2008). For nonallergic rhinitis, the scoring can generally be much more straightforward.

Pediatric versus adult patients

Patient-related outcome measures for young children are almost always indirect: recorded by the caregiver. Consequently, PRO variables depend not only on the child's symptom burden, but also on the parental interpretation of how much the symptoms affect their child. A worried parent might overestimate and a working parent who has little contact with the child during the daytime might underestimate the severity. In trials with young children, this third-party bias is always present. Investigators might try to reduce bias by asking two or three of the child's caregivers to independently fill in the scoring and to have built-in internal validation in the questionnaires. In this respect, the results from a longitudinal birth cohort study on atopic diseases, involving 411 children (born between 1999 and 2001, to asthmatic mothers),

are encouraging. Investigators re-evaluated the data obtained in biannual parental interviews of the Copenhagen Study on Asthma in Childhood (COPSAC) against the medical events reported by their family practitioners. The findings supported the validity of data obtained on medical events by parental interviews [11]. However, no scoring of severity was evaluated here.

The nature of the intervention being evaluated

The suitability of a specific outcome measure depends on the kind of intervention that is being analyzed. Thus, for an evaluation of outcome measures, we shall first need to define the groups of interventions being studied in the management of rhinoconjunctivitis in children.

The interventions used in the overall management of rhinoconjunctivitis in children can be roughly divided into three groups:

- (1) Environmental control
- (2) Medication: topical and systemic
- (3) AIT (specifically in the subgroup of ARC)

Environmental control

Interventions in each of the three areas (1-3) mentioned above can be expected to have beneficial effects not only in the nose, but also in other organs affected by allergy. Even topical nasal treatment has been shown to improve symptoms of allergic conjunctivitis. Just as impairment of upper airway breathing negatively influences the lower airways, a principle acclaimed worldwide by the ARIA (Allergic Rhinitis and its Impact on Asthma) initiative [12] indicates that improved nasal patency could be expected to enhance bronchial symptoms [13]. Thus, scoring of nasal symptoms might not capture the whole image of efficacy, as already commented above. The authors would like to argue that for environmental control measures in allergic children, the picture is even more complex. The caregivers are generally those who have to apply control measures, which are actions that take effort, time, and costs, factors that could influence the parental evaluation of their child's symptoms. After accomplishing several of the control measures, caregivers might be more likely to estimate their protege's symptoms as improved. An additional factor to consider is that a lot of parents suffer from allergies themselves; the environmental control measures might make them feel better and this might again positively influence the way they score their child's symptoms.

Medication

If the intervention is pharmacotherapy, a combined nasal-ocular symptom score might suffice. The ocular symptoms should be included even in topical nasal medication, as they can have some effect on the eyes as well, as demonstrated with the use of intranasal steroids [14].

Allergen immunotherapy

In addition to favorable results for all allergic symptoms – on top of nasal symptoms – the evaluation of the full dimension of benefits from AIT has several other pitfalls. Firstly, in immunotherapy trials, patients in both active and placebo groups are normally allowed to take medication in case their symptoms become out of control. Thus, the positive effects of immunotherapy have to be demonstrated on top of the pharmacotherapeutic effects, which is crucial to bear in mind when evaluating improvement with immunotherapy. When AIT trials report a 20–25% improvement in the patient's total symptom-medication scores compared with the placebo, readers should pay attention to the improvement in the placebo group as well, which reflects the true placebo effect and the effect of taking allowed (rescue) medication [15²²]. As a consequence, the patients on AIT do not improve 20–25% in their scores, but 20–25% on top of their prior improvement facilitated by pharmacotherapy. Evaluating results of clinical trials on AIT in this light makes the real total gain for the patient more visible, and is a clear rebuttal to the negative comments on AIT sometimes heard, eluding to a rather 'poor' effect shown by trials for 'such a costly treatment'. Second, patients often experience a mild flare in symptoms during the first stages of immunotherapy, as its full effect takes weeks to kick in [16,17]. Consequently, AIT trials always have to be long-term, which makes trials costly and drop-out rates high, especially in the placebo groups. Third, AIT reduces symptoms and medication intake not only during the treatment, but also for several years after discontinuation [18²³,19]. Finally, it is common knowledge that AIT in children with allergic rhinitis reduces the prevalence of asthma, even years after treatment [20]. To show this disease-modifying effect, trials should be of at least 3 years with a follow-up period after that [21].

As such, a head-to-head comparison of the improvement in Nasal Symptom Score between a pharmacotherapeutic agent and AIT is not plausible, nor fair, as the effect of immunotherapy goes beyond the sole, short-term improvement of the ocular and nasal symptoms.

Symptoms beyond rhinoconjunctivitis: comorbidities and health-related quality of life

ARC is often accompanied by comorbid asthma. Some studies report an almost 50% rate of comorbidity, which is even more frequent in the pediatric age group [22]. Also, in patients allergic to certain allergens, the nose and lung tend to react as one united organ, giving rise to nasal and bronchial symptoms together, for example, house dust mite, cat, and *Alternaria*, to name a few. Further impact of allergy on the general well being and quality of life, and the benefit of systemic treatments, especially AIT on this aspect, are commented on in the section below. Thus, in the evaluation of efficacy of certain interventions in children with ARC, it is often impossible to take only nasal and ocular symptom and medication scores into account, as this only covers part of the intervention's effect.

Scoring systems for patient-related outcomes and quality of life

Once the investigator has defined the kind of rhinoconjunctivitis to be studied, the age group on which to focus, and the nature of the intervention, the investigational team has to select the specific outcome measures. We discuss several of them below.

What is being scored?

In Table 2, we present some of the scoring systems used to score symptoms, including organ-specific, combined, and more general symptom scoring systems. Some of the tools have tried to include the effect of medication on symptoms into the scoring system, an attempt to enhance the previously used Total Combined Symptom-Medication Score (TCSMS).

A pilot study showed the poor performance of 7–9-year-old asthmatic children in self-assessing their upper airway functioning. Investigators related the actual values of upper airway flow measured through a portable nasal peakflow meter the children were taught to use, with their perceived nasal obstruction as reported by the children in their diaries. Both measures were poorly correlated, indicating the difficulty children have in assessing their nasal patency correctly [26].

Roder *et al.* [27^{***}] analyzed the relevance of several pediatric patient-related outcomes using data of a trial on grass pollen sublingual immunotherapy in children with rhinoconjunctivitis (see 'Quality-of-life questionnaires'). Analyzing the retrospective Global Assessment of Symptoms (GAS)

against actually reported data in the patient diaries, they found GAS did not sufficiently reflect the actual symptoms during the preceding season.

Recently, some investigators proposed a different approach, focusing on control of the rhinitis symptoms, similar to that which has been done with asthma. In a very complete review, several Rhinitis Control Assessment instruments (see bottom part of Table 2) were discussed [28[•]]. The benefit of centering on control as one of the main outcome measures might change the scope of the physician–patient relationship, away from the more restricted focus on symptoms, symptom severity, and medication, to the more complete well being of the patient. Finally, it is not the severity of the symptoms that affects the patient's health, but the interpretation of the patient of his/her symptoms and the extent to which the patient feels to not be well controlled. As such, it was commented by ARIA members in two recent papers that disease control shall be considered in future initiatives of the group, stressing that the methods for measuring control should be uniform [29]. One of the counter sides of only measuring control is that medication intake is not taken into account in this measure. A patient may be very well controlled while taking antihistamines and intranasal corticosteroids, but this does not make him a mild patient. Thus, if control is considered as a useful PROs, medication score should always be measured as well. Moreover, these tools until now have not been evaluated in children.

Quality-of-life questionnaires

As we have already discussed above, children with ARC do not only have eye and nose symptoms, as allergy is a systemic disease that affects many aspects of health, including general well being, quality of sleep, concentration, and fatigue [30]. As such, quality-of-life questionnaires are now recommended by both the GA2LEN and the World Allergy Organization (WAO) to form an integral part of the evaluation of patients recruited in immunotherapy trials [2,21].

A Dutch team analyzed the relevance of the disease-specific rhinoconjunctivitis quality-of-life questionnaire (RQLQ), the generic COOP/WONCA charts, and a GAS based on data from a previously conducted trial among 6–18-year-old children published by the same team [31]. They choose the COOP/WONCA charts that measure the functional health status, because they are short six-item questionnaires, in which the answers are illustrated with a drawing, ideal for the pediatric age group and they appear to have low susceptibility to cultural differences. Investigators considered a patient-related

Table 2. Patient-related outcomes used in AIT trials

What is scored	Scoring	Comments
Nasal symptoms	Total Nasal Symptom Score (TNSS): 4 nasal symptoms (sneezing, rhinorrhea, pruritus, obstruction), each on a 0–3 scale	
	Nasal Symptom Score:	
	5 nasal symptoms, including hyposmia	
	VAS of nasal symptom severity:	
	Not separated per symptom	
	Average Adjusted Symptom Score:	This tool was validated post-hoc with the results obtained in an adult grass-pollen immunotherapy trial [7]
	Adjusts the TNSS according to intake of rescue medication. ^a	
Eye	Total Conjunctival symptom score (TCSS):	
	3 eye symptoms (redness, pruritus, lacrimation) each on a 0–3 scale	
	Rhinoconjunctivitis Total Symptom Score:	
	As part of the total nasal symptom score: this becomes then a six-item score	
Eye-Nose-bronchi	Allergy-Control-SCORE:	Validated in adults [5]
	10-item symptom scoring system, taking into account eye, nose, and bronchial symptoms, all scored on a 0–3-point scale. This system adds an adjusted daily medication score to the symptom score	
Global	Global assessment of symptoms (GAS):	A tool used to select participants with sufficient symptoms during the preceding season for clinical trials (retrospective). Low correlation with diary data [27 ^{***}]
	Retrospective global evaluation by the patient of his symptoms over the preceding allergen exposure season	
	Patient-relevant treatment benefit:	Validated and feasibility was tested in adults [8]
	On a 25-item questionnaire, the patient rates which of these are more-less important to him/her. At the end of the treatment, the patient rates the extent to which these needs were achieved. With computer program, a Patient Benefit Index is calculated	
Control	Control of Allergic Rhinitis and Asthma Test (CARAT):	Validated in adults [23]
	6-item self-assessment tool for allergic rhinitis and asthma over previous 4 weeks	
	Allergic Rhinitis Control Test:	Validated in adults [24]
	5-item self-assessment tool for allergic rhinitis over previous 2 weeks. Cut-off: 20	
	Rhinitis Control Assessment Test	Validated in adults [25]
	5-item self-assessment tool for allergic rhinitis over previous week	

^aTo calculate the Average Adjusted Symptom Score (AdSS), the RTSS is adjusted as follows: if a patient takes rescue medication on day d, the day's AdSS [AdSS(d)] is defined as the value of RTSS(d) or AdSS(d–1), whichever is higher. The AdSS on the following day [AdSS(d+1)] is defined as the value of RTSS(d+1) or AdSS(d), whichever is higher.

outcome as relevant if it was responsive to pollen exposure and if it had a moderate-strong correlation with the classical symptoms of ARC. They classified as relevant patient-related outcomes for the monitoring of children and adolescents with grass

pollen rhinoconjunctivitis: the pediatric [32] and the adolescent [33] RQLQ, but not the COOP/WONCA charts. It was commented that the RQLQ could be shortened as 40% of the items did not meet the investigators' criterion of relevance, but that a

validation of the mini-RQLQ for children and adults should be conducted in two groups of patients, not only in those with allergy to pollen, but also in those with allergy to indoor allergens [27^{***}].

Timing and frequency of patient-related outcome scoring

Depending on the patient-related outcome selected, the timing and frequency of measuring have to be defined (see Table 3). Here several parameters have to be considered. For completeness of the data-set and better statistical results in clinical trials, investigators should strive for the best possible patient compliance in filling in patient related outcome questionnaires. In this respect the best results can be obtained with a user-friendly tool, with nice layout, that takes little time to be filled-in and that has to be completed only over the time-span of a couple of days/weeks (see Table 3). In some pharmacologic trials, symptom scoring is often done twice daily [34]. On the diary charts, it should be stated clearly whether it is the instant symptom or the 12-h reflective symptom scoring. The shorter and easier to use the tool, the less burden the study poses on the study participants. For adolescents and young adults, iphone applications with the questionnaire might be a solution.

However, if the tool is longer and completing needs some extra effort, daily scoring is not possible. In such a case, scoring can be done over several days during a certain time-span at the beginning of the trial, half-way, and at the end. Here the trade-off between less data-better patient compliance versus more data, better statistics, has to be thoroughly discussed with the study team, including the statistician.

Patient-related outcomes in pediatric rhinitis trials over the past 16 months

To put the issues discussed above in context of recently presented data in children, we did a *Pubmed* search of published original articles on rhinitis or rhinoconjunctivitis in children with allergic rhinitis, in which some patient-related outcomes were reported. The search terms child* OR pediatri* OR paediatr* AND rhinitis, and child* OR pediatri* OR paediatr* AND rhinitis AND outcome were used, within the search limits of October 2012 to February 2014. We analyzed which patient-related outcomes were scored (see Supplementary Digital content 1, <http://links.lww.com/COAI/A7>). We found a total of 24 trials, but excluded two because their main focus was on pediatric asthma; in one trial, there was no separate presentation of pediatric data and one was a review article.

Some variant of symptom scoring was reported by 18 of the 20 studies. This was mostly the four-item (blocked nose, pruritus, sneezing, and runny nose) 0–3-point scale. In one of the trials, only the question on presence or absence of nasal or nasal-conjunctival symptoms was interrogated [from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire]. In another trial, only symptom scores after a nasal provocation test were investigated. In all immunotherapy trials, some form of medication scoring was included. Two of the 20 trials evaluated the nasal symptom severity with a Visual Analogue Scale and one used the rhinitis control assessment test (see above). One study included attention-deficit-hyperactivity-disorder symptom scale and a computerized continuous performance test for attention and impulsivity. Here, patients with allergic rhinitis were at higher

Table 3. Patient-related outcome scoring: how often and during how many days/weeks?

Frequency of scoring per day	Once daily
	Twice daily
Which symptoms should be described?	Instant symptoms (= those present at the very moment of scoring)
	Reflective symptoms (= those that have been present over the past XX period, normally 12 or 24 h)
Time span during which tool is completed	Once
	1–2 weeks
	1 month
	Continuously
Frequency of scoring over a longer period of time	Once or during 1–2 weeks every 3 months
	Once or during 1–2 weeks every 6 months
	Once or during 1–2 weeks every 12 months
	Once or during 1–2 weeks every 18 months
Tool characteristics make frequent testing more or less feasible	Short 1-page questionnaire/chart, electronic record
	Quality-of-life questionnaire: needs more time

risk to suffer from some kind or another of attention deficit and/or impulsivity [35]. Finally, a pediatric quality-of-life tool was included in 10% of the trials; in one, this was considered as the primary efficacy parameter, together with the Total Nasal Symptom Score [36].

The authors realize this search is not a complete search, which would go beyond the scope of this article, but our aim was to give some idea to the reader about the reporting of PRO in pediatric clinical trials on rhinitis over the previous year.

CONCLUSION

The subjective patient-related outcomes have been until now the sole primary outcomes of clinical trials in adults and in children with rhinoconjunctivitis. Especially in ARC, not only the nose and eyes are affected, but also a general feeling of malaise and fatigue is frequently present as is comorbid asthma. Consequently, mono-organ symptom scoring systems are no longer recommended [37]. This opens the window for new tools with a broader basis. Several have been reviewed in this article, but lack validation in children. The EAACI issued a position paper on general recommendations for the standardization of clinical outcomes used in AIT trials for ARC, but without a specific focus on children [38]. In the literature review of the last year, one article showed the good correlation of the pediatric and adolescent RQLQ questionnaires with pollen counts and Total Nasal Symptom Score. Actually, in this study, a 40% reduced RQLQ would have performed just as well. It could be argued whether the most complete way to evaluate allergic patient's improvement in rhinoconjunctivitis trials would be with a mini-RQLQ combined with medication scoring and whether this tool should be upgraded to a primary efficacy outcome measure [39].

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Conflicts of interest

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