

EDITORIAL

Assessing rhinitis symptoms in children – a need for action

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Allergic rhinitis, one of the most prevalent chronic diseases in childhood, is developing early in life with the highest annual incidence between 3 and 10 years of age (1). Several cohort studies have carefully evaluated the process of allergic sensitization and subsequent development of nasal and conjunctival symptoms such as itch, hypersecretion, photophobia, and blocked nasal breathing (2–5).

Obviously, many children become symptomatic at an age when they can neither read nor write. Therefore, they have to rely on caregivers when it comes to describing subjective symptoms, a problem which was clearly underestimated in the past.

The paper by Berger et al. in this issue of PAI (6) assessing the efficacy and safety of a new class of AR medication clearly demonstrates that the influence of parents or caregivers on reporting patient-related outcomes in young children deserves a closer look, as this important confounder may have strong impact on study results. The efficacy of MP29-02 (a novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP) in a single device), is already well established in adult and adolescent AR patients (7). The pediatric AR trial reported here may be used to better understand the complexities involved with conducting trials in children and to investigate methods of symptom assessment in this population. In particular, quality of life was assessed by all children themselves using the PRQLQ, but symptom severity was recorded by either patients or caregivers.

Role of EMA in pediatric trials

The European Medicines Agency (EMA) plays an important role in the development of medicines for children. In the past, authorized medicines in Europe were not adequately studied and subsequently not authorized in children. To rectify this situation, the European Union's Paediatric Regulation (which came into effect in 2007) gave new responsibilities to the EMA to stimulate research into uses of medicine in children. The aim was to authorize medication use in all ages (if appropriate) and to improve the health of children in Europe (8, 9). Since then, the EMA and its pediatric committee have agreed on more than 600 pediatric investigation plans and have successfully

encouraged the undertaking of more pediatric trials than ever before (approx. 350–450/year, including children aged 0–18 years) (10), making investigations in the pediatric population a more integral part of medicinal product development in the EU.

Lack of validated instruments

Although the EMA and the Food and Drug Agency (FDA) request studies on children aged 5–11 years of age, they do not recommend tools specifically adapted for this age group. Patient-reported outcomes (PROs) have been proposed in allergy (11) but not for children. Indeed, clinical trials conducted in children with allergic rhinitis (AR) should be interpreted with caution, as most currently used PROs give a restricted view (12). The Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) has been developed specifically for children, (13) but it has been used in randomized controlled trials (RCTs) (4, 5) and the magnitude of difference by comparison with the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) for adolescents and adults is not clear.

Problems associated with clinical trials in pediatric subjects with allergic disease

In allergic diseases, many studies have been carried out in preschool and school-age children (14–17). Difficulties associated with pediatric trials have been summarized in a recent GA²LEN-ARIA statement related to sublingual immunotherapy (SLIT) in children, but its conclusions apply to all trials in preschool and school children. They include (i) difficulties inherent to RCTs in patients with allergic disease (e.g., design flaws, under-powering, compliance), (ii) the high placebo effect in RCTs in all age groups (in both pharmacotherapy and immunotherapy trials), and (iii) the fact that treatment effect size is traditionally smaller in children as compared to adults, a point well made in a recent meta-analysis on efficacy of SLIT (18). A similar reduced treatment effect size has been observed in intranasal corticosteroid (INS) or H1-antihistamine efficacy trials in children (15–17) vs. adults.



Figure 1 Time to achieve $\geq 50\%$ change from baseline in reflective total nasal symptom score according to degree of child self-rating in children aged 6–11 years with moderate/severe SAR.

Need for action

There are three major confounders in pediatric AR trials that may account for the reduced treatment effect compared to adults.

- In pediatric AR trials, caregivers frequently assess nasal and ocular symptoms by proxy. To date, there is no comparison between caregiver and patient symptom severity assessments, and so whether caregivers can accurately assess impact of disease remains unknown (Fig. 1a,b).
- Children seem to report less severe (or briefer) symptoms than adolescents and adults, although again no comparisons are available. This limits recruitment of a symptomatic study population, in particular in very young children.

- Allergic sensitization and allergic disease are not finally established before adolescence (2). This may increase variation and consequently reduce study sensitivity.

It seems that there is an urgent need to compare allergic rhinitis RCT results (for both pharmacotherapeutic and immunotherapeutic interventions) between adolescents/adults and children (5–10 years of age) in order to develop PROs specifically for children. Validation of the assessment of outcomes will have to include sensitivity to intervention in younger children who are not yet able to read or write. The leading scientific society, particularly the active pediatric allergists, should realize this challenge and generate novel tools to assess allergic rhinitis symptoms in young children.

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