House dust mite induced allergic rhinitis in children in primary care

Epidemiology and Management

Cindy de Bot

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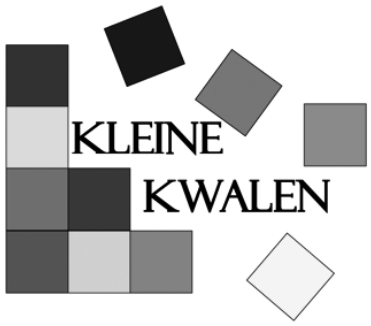

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Epidemiologie en Management

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Chapter 1

General introduction

ALLERGIC RHINITIS

Allergic rhinitis (AR) is an allergen-induced, upper-airway inflammatory disease. The characteristic symptoms of allergic rhinitis are a runny nose, sneezing, congestion, redness of the eyes, watering eyes, and itching of the eyes, nose and throat.[1,2] Previously, allergic rhinitis was subdivided into seasonal and perennial allergic rhinitis. The current classification of the World Health Organization (WHO) subdivides allergic rhinitis into intermittent allergic rhinitis and persistent allergic rhinitis (ARIA Guidelines).[3] Intermittent allergic rhinitis occurs in people who are allergic to grass or tree pollen present during spring and summer (hay fever). Persistent allergic rhinitis results from the constant presence of allergens such as mold, animal dander or house dust mites. This type of allergic rhinitis occurs throughout the year, although symptoms may be less severe than with intermittent allergic rhinitis.[3]

This thesis focuses on persistent allergic rhinitis triggered by house dust mites in children. The majority of patients who seek medical advice visit their general practitioner.[4-6] Although allergic rhinitis is not a life-threatening disease, it can have a significant effect on quality of life, and is associated with a number of common co-morbidities, including asthma and sinusitis.[2,3,7]

Prevalence of allergic rhinitis

Allergic rhinitis affects between 15% and 20% of the population [3], thereby constituting a serious public health problem in our society. In most epidemiological studies, no distinction is made between intermittent allergic rhinitis and persistent allergic rhinitis.[8-15] High prevalence rates are reported from several regions, such as Canada, Australia, the USA and Europe.[16] The prevalence of allergic rhinitis, asthma and other allergic conditions (such as eczema) has been increasing worldwide over the past decades.[8,9] Many epidemiological studies have investigated the change in prevalence of childhood allergic rhinitis and asthma. From a recent ISAAC study (2009), using a standardized epidemiological method to survey the prevalence of allergic rhinitis in children (aged 6-7 years and 13-14 years) from 236 centers in 98 countries worldwide, the prevalence ranges from 1% to 45% worldwide.[16] For example, in Scottish children over a 25-year period, the prevalence rose from 3% in 1964 to 12% in 1989.[10] Among Swedish schoolchildren, the prevalence of allergic rhinitis, asthma/wheeze or eczema increased continuously from 24% to 33% between 1979 and 1991.[11] Hakansson and colleagues reported an 11% increase (from 12-23%) in the prevalence of rhinitis among Danish children between 1986 and 2001.[12] Other studies in Europe also showed an increase ranging from 9% to almost 26% in children and adolescents.[13,14] In Italy, Galassi and colleagues reported an increase in prevalence of allergic rhinitis among children (increase from 14-19%) and adolescents (increase from 32-35%) in the period 1994-2002.[15]

Environmental factors such as increased air pollution, changed lifestyle, and a decrease in bacterial/viral infections are frequently reported as risk factors for allergic sensitization and possible causes of the increased prevalence; also the 'hygiene hypothesis' has been proposed as a possible explanation.[17-20]

Thus, time trends in asthma and allergic rhinitis have shown a substantial increase since the early 1960s until the 1990s. More recently an increasing number of studies reported reversing trends or a plateau phase of childhood asthma and atopy since the late 1990s.[21] For example, Braun-Fahrlander and colleagues reported that no further increase in asthma and allergy rates occurred during the 1990s in adolescents living in Switzerland.[22] The review of Gupta et al. showed that the prevalence and healthcare usage for hay fever in the UK had increased substantially over recent decades, but was now stabilizing or even falling since the late 1990s.[23] Also, a study in southern Germany reported no further increase in the prevalence of asthma and atopy in 10-year-old children in the period 1992-2001.[24]

The underlying reasons for the decrease or plateau in prevalence of asthma and atopy remain unclear. Although factors such as increased professional awareness of asthma/atopy, earlier detection, and improved treatment are reported as possible causes of changed trends in prevalence of atopy and asthma.[26] Others hypothesized that exposure to environmental factors, summarized as 'Western lifestyle', intensified during the 1950s and 1960s and remained fairly constant during more recent years, thus no longer influencing the time trend of asthma and allergies in cohorts born in the 1980s.[22]

Clinical presentation

Allergic rhinitis typically presents before age 20 years. The average age of allergic rhinitis onset is 8-11 years and symptoms are usually evident by young adulthood. Boys up to the age of 10 are twice as likely to have symptoms of allergic rhinitis as girls.[2,3] Children with a family history of rhinitis and first-born children are predisposed to develop allergic rhinitis, and are also more likely to have asthma and atopic eczema.[26-28] The duration and severity of allergic rhinitis symptoms is different in every patient.[29,30] Patients can be severely restricted in their daily activities, resulting in excessive time away from work or school and decreased quality of life.[31,35,36] For children, allergic rhinitis can take a substantial toll on their general wellbeing and school performance.[31-34] Adults and children often have a poor quality of sleep, may suffer from obstructive sleep apnea and experience daytime fatigue.[35,36] From a survey in Europe, Canoni et al. reported that about 80% of patients indicated that allergic rhinitis had at least some impact on their daily lives, and for 13% of patients this impact was moderate or severe. About 50% of patients reported that their symptoms of allergic rhinitis had some impact on their sleep patterns.[36] The economic burden of allergic rhinitis is substantial. For example, in the USA it is reported that in 2003 the annual cost of allergic rhinitis ranged from $US 2-5

billion.[37] In Sweden, the cost of allergic rhinitis is 2.7 billion euro per year in terms of lost productivity.[38] Costs are not restricted to impaired physical and social functioning, but may also entail a financial burden such as medication costs and visits to health practitioners.[36,39]

If allergic rhinitis remains unrecognized or undiagnosed, this may result in inadequate control of symptoms. Surveys in Europe and the USA reported that allergic rhinitis was undiagnosed in about one-third of adults with the condition, and that only about 12% of people with allergic rhinitis sought prescription treatment.[40,41] Therefore, allergic rhinitis management should focus on meeting patients' needs for a rapid, long-lasting and convenient treatment of allergic rhinitis.[3,7]

DIAGNOSIS AND MANAGEMENT OF ALLERGIC RHINITIS

Allergic rhinitis is diagnosed by the patient's history in combination with physical examination and/or specific allergy tests, either the skin prick test or blood tests for specific IgE.[3,7,42] The management of allergic rhinitis includes patient education, avoidance of allergens and pollutants (e.g. tobacco smoke), pharmacotherapy and allergen-specific immunotherapy. The ARIA guidelines mention the following pharmacotherapeutic options for allergic rhinitis: antihistamines, corticosteroids and decongestants. Medications used for allergic rhinitis are most commonly administered intranasally or orally.[3,7,42]

As shown in Figure 1.1 [43], oral antihistamines are often the first-line therapy for mild-to-moderate allergic rhinitis. Antihistamines work well for treating allergy symptoms, especially when symptoms do not occur very often or do not last very long. Corticosteroid nose sprays can be used if rhinitis symptoms are chronic or if symptoms are moderate to severe; they work best when used continuously, but can also be helpful when used for shorter periods of time.[3,7,42] Decongestants may be helpful in reducing symptoms such as nasal congestion and are used for mild-to-moderate allergic rhinitis complaints.[3,7,42] If allergen avoidance and medical treatment for allergic rhinitis are not effective, allergen immunotherapy may be an option. Small amounts of the allergen are given regularly, while slowly increasing the dosage until a plateau is reached, followed by a maintenance phase.[44,45]

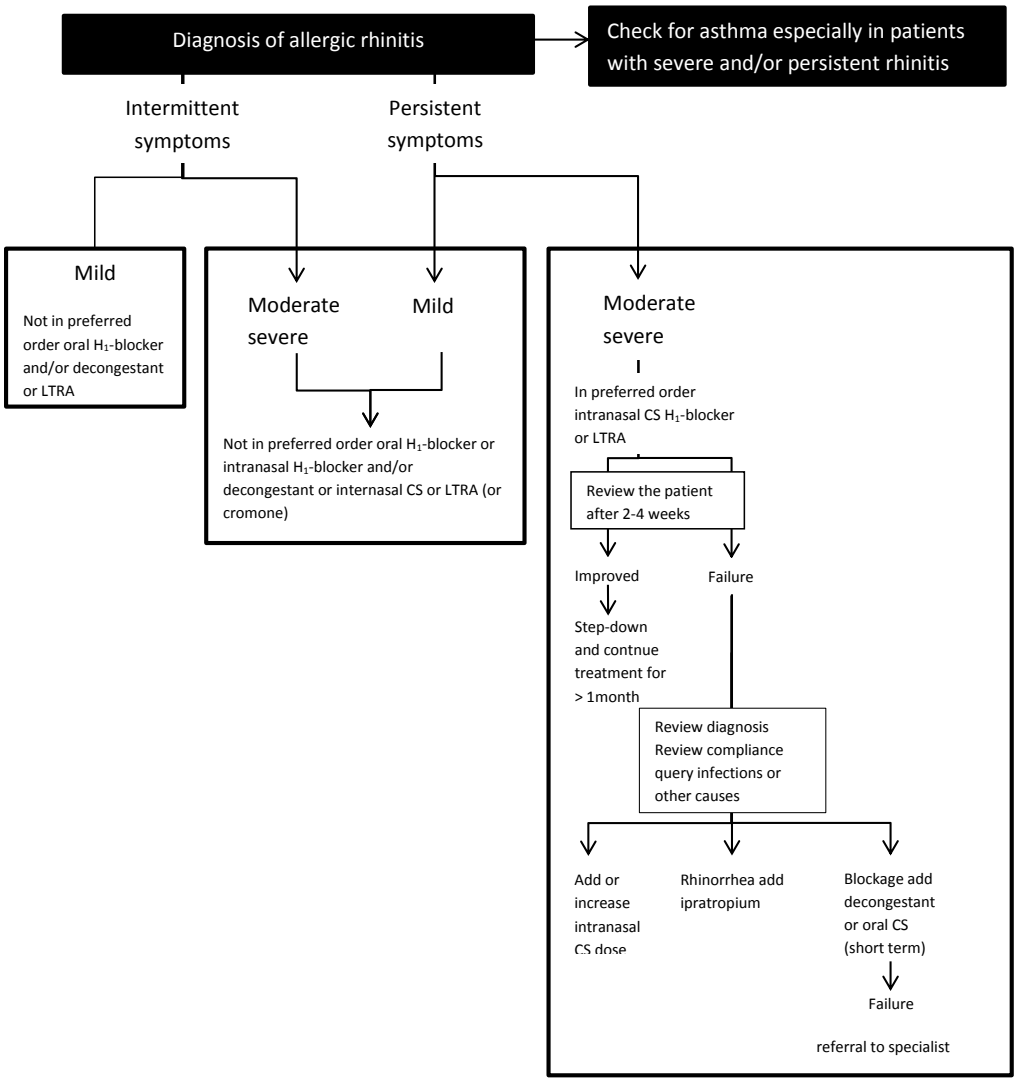

Figure 1.1: Treatment options for allergic rhinitis according to the ARIA guidelines.[43]

Dutch primary care guidelines versus ARIA guidelines

The majority of patients with allergic rhinitis and asthma are treated by primary care physicians, as in the Netherlands, but also in, e.g., Belgium, France, the UK and the Scandinavian countries.[4,46-48] Interaction in the management of allergic rhinitis between primary care physicians and allergy specialists has been encouraged.[49] This has resulted in specific guidelines for treatment and management of allergic rhinitis in primary care, as the spectrum of patients with allergic rhinitis in primary care may differ from those under specialist care.[50,51] The ARIA guidelines were the first evidenced-based guidelines developed together with primary care physicians.[3,7,42]

The ARIA guidelines for treatment of allergic rhinitis are different in some aspects of treatment compared to the guideline of the Dutch College of General Practitioners ('Allergic and non-allergic rhinitis').[52] The practice guideline 'Allergic and non-allergic

rhinitis' of the Dutch College (1995) was revised in 2006 based on recent developments.[52,53] The revised practice guideline uses the international terminology of 'intermittent allergic rhinitis' and 'persistent allergic rhinitis'. The management of allergic rhinitis includes patient education, avoidance of allergens and pollutants (e.g. tobacco smoke) and pharmacotherapy.

The Dutch guideline recommends a smaller spectrum of pharmacotherapy. Local or oral antihistamine and/or corticosteroid nose sprays are advised for mild intermittent symptoms of allergic rhinitis. For moderate/severe persistent symptoms of allergic rhinitis, a corticosteroid nose spray is recommended.[52] The most important difference between the Dutch practice guideline and ARIA guidelines is the use of leukotriene receptor antagonists (LTRA). LTRA are associated with very limited therapeutic value and not recommended as treatment in the Dutch guideline.[52] In contrast, the ARIA guidelines suggest LTRA as treatment for mild to severe, intermittent symptoms of allergic rhinitis (Figure 1.1).[43] Sublingual immunotherapy is not recommended in the Dutch guideline, because the evidence for the effectiveness of sublingual immunotherapy is inconclusive.[53] The ARIA position paper accepted the use of sublingual immunotherapy in adults and children as a valid alternative to subcutaneous immunotherapy.[45]

ALLERGEN IMMUNOTHERAPY

The history of specific allergen immunotherapy spans almost 100 years. In 1911, Noon and Freeman described conjunctival provocation of patients with allergic rhinoconjunctivitis and successful treatment using subcutaneous injection with allergen.[54,55] Allergen immunotherapy involves the repeated administration of increasing quantities of specific allergens to patients with IgE-mediated conditions until a dose is reached that is effective in reducing disease severity from natural exposure. Allergen immunotherapy reduces responses to allergic triggers that precipitate symptoms, decreases inflammatory response, and could prevent development of persistent disease in the long term.[45] During the 1990s other routes were investigated, involving sublingual application, the nasal route, or oral administration (sublingual tablets).[45] Specific immunotherapy with allergens might prevent the onset of asthma and new sensitizations in children with allergic rhinitis.[56,57] Some studies suggest that specific immunotherapy with allergens is also preventive for development of asthma in children with allergic disease.[58-61]

Since its discovery, immunotherapy, administrated subcutaneously (SCIT), has been the most used route for several decades and is effective in adults.[62] However, in children the evidence remains inconclusive.[63,79] The disadvantages of subcutaneous immunotherapy are the unpleasant injections and the potential risk of serious side-effects

such as systemic reactions, ranging from rhinorrhea to severe asthma and anaphylactic shock.[65,66]

Sublingual immunotherapy is more convenient than subcutaneous immunotherapy and has a good safety profile.[64,66,67] In 1998, the WHO concluded in a position paper that sublingual immunotherapy is a viable alternative to the injection route and that its use in clinical practice is justified.[45] Allergen immunotherapy is recommended in the ARIA guidelines for patients with more severe disease, for those not responding to usual treatments, or for those refusing usual treatment.[3,7] Sublingual immunotherapy is frequently used in European countries, especially in the Mediterranean regions.[68,69]

Curtis suggested the sublingual application of immunotherapy as early as 1900.[70] Not long after this suggestion, grass pollen extracts were administered by oral route and reported in 1927.[71] Clinical use of sublingual immunotherapy for foods was described in 1969 by Morris and in 1970 for inhalant allergens.[72,73] The first randomized, double-blind placebo-controlled study of sublingual immunotherapy (using a house dust mite allergen) was published in 1986.[74] Since the mid-1980s several controlled trials using sublingual immunotherapy (SLIT) have been published with different outcomes in effectiveness, and summarized in systematic reviews and meta-analyses.[75-79]

Sublingual immunotherapy with grass pollen and tree pollen allergen in children

Despite its wide use, the evidence for sublingual immunotherapy with grass pollen and tree pollen allergen in children was still inconclusive. Wilson et al. reported no significant reduction in symptoms and medication scores in those studies involving only children, but the total number of participants was too small to make this a reliable conclusion.[79] In this latter Cochrane review, the evidence for efficacy for immunotherapy was supported for adults, in accordance with others.[98] However, Röder et al. reported insufficient evidence for efficacy of immunotherapy in any administration form in children and adolescents with allergic rhinoconjunctivitis.[63] After publication of these reviews, four high-quality articles were published.[80-83] Three trials showed positive effects of sublingual immunotherapy with grass pollen allergen in children in two trials and one trial with tree pollen. One trial with sublingual immunotherapy with grass pollen extract in primary care found no effect.[82]

These large studies with sublingual immunotherapy tablets in grass and tree pollen allergic children showed the efficacy and safety with more confidence. The trial reported by Vilovirta et al. with sublingual immunotherapy with tree pollen extract showed a significant reduction of symptom ($p=0.01$) and medication scores ($p=0.04$) compared with placebo.[80] One trial using sublingual tablets with grass pollen extract reported that a mean improvement for the rhinoconjunctivitis total symptom score of 28.0% was seen compared with placebo.[81] The other trial reported by Bufe et al. showed that the

rhinoconjunctivitis symptom scores and medication scores and the asthma symptom score were all statistically significantly different between the two treatment groups. The differences in medians relative to placebo were 24%, 34%, and 64% in favor of active treatment.[83] However, Röder et al. studied sublingual immunotherapy with grass pollen extract in primary care and found no difference between verum and placebo.[82]

A recent meta-analysis of Di Bona et al. (2010) reported data suggesting that sublingual immunotherapy with grass pollen allergens is not of particular benefit for children, showing only a small effect both for reduction of rhinitis symptoms and anti-allergic medication compared with placebo.[85]

However after 2010, several large randomised trials in children were published that contribute to a shift towards a positive balance of evidence for sublingual immunotherapy in children, mainly for grass allergens.[84,86,87]

Sublingual immunotherapy with house dust mite allergen in children

Randomized double-blind placebo-controlled trials in children with house dust mite allergen have accumulated in the last years, but the total numbers of participants with house dust mite allergy were small.[89-92] The efficacy of sublingual immunotherapy with house dust mite allergen remains inconclusive given the diverging conclusions of trials in children.[88,97]

In 2004, a systematic review showed that sublingual immunotherapy was moderately effective in children older than 4 years, with mild asthmatic symptoms or rhinoconjunctivitis due to house dust mite sensitization.[93] Recently, Hoeks and colleagues published a review of five randomized double-blind placebo-controlled trials with house dust mite allergic children.[94] Their main finding related to the effectiveness of sublingual immunotherapy in children, was a reduction in asthma symptom score to house dust mite allergy in the intervention group compared with the placebo group, but not in medication use. They found no decrease of allergic rhinitis complaints.[94] Whereas there is substantial evidence regarding the effectiveness of sublingual immunotherapy on pollen allergy in children, the efficacy on house dust mite allergy in children is less straightforward, as some well-conducted trials show inconsistent results.[95] A meta-analysis of Compalati et al. found promising evidence of sublingual immunotherapy using house dust mite extract in allergic patients suffering from allergic rhinitis and allergic asthma.[96] They included eight studies with pediatric subjects (aged 5-18 years).[96] In another review, the authors described the current international expert recommendations for the use of allergen-specific immunotherapy for respiratory allergies and analyzed what was needed for the future.[97] In accordance with other reviews, they recommend to perform large well-designed clinical trials to establish the clinical efficacy and safety of sublingual immunotherapy with perennial allergens (mainly house dust mite) in children.[88,96,97] In 2010, an open randomized controlled trial was performed, comparing sublingual

immunotherapy, subcutaneous immunotherapy and pharmacotherapy in relation to clinical efficacy and immunological mechanisms in asthmatic/rhinitis children who were sensitized to house dust mite. It was concluded that both sublingual immunotherapy and subcutaneous immunotherapy demonstrated clinical improvement compared with pharmacotherapy in children with asthma/rhinitis sensitized to house dust mite, however only 16 children received sublingual immunotherapy.[99] Another retrospective observational, monocenter study indicated that high-dose SLIT with house dust mite allergen in children (n=78) with rhinitis caused by house dust mites was well-tolerated and could be an effective treatment. Patient evaluation of allergy severity and medication use revealed a highly significant improvement between baseline and six months ($p<0.001$). This improvement on both items was maintained throughout the four-year follow-up period.[100] Although these trials appear promising, they do not comply with the recent guidelines for performing and reporting trials in specific allergen immunotherapy.[101]

ALLERGIC RHINITIS: RELATIONSHIP WITH QUALITY OF LIFE

The definition of health-related quality-of-life by Schipper et al. as `the functional effects of an illness and its consequent therapy upon a patient, as perceived by the patient' emphasizes the importance of the patient's view.[102,103] Allergic rhinitis is a chronic inflammatory disease of the airways that can diminish a person's quality of life. Nasal obstruction is, for example, a crucial symptom in allergic rhinitis, and is associated with sleep disturbances, and impaired performance at school and work.[3,7,42] Although patients are troubled by particular symptoms, it is often the impact of these symptoms on their day-to-day activities that causes them to seek medical help.[33,35] The impact of rhinitis on quality of life is often underestimated.[34] The guidelines of the Allergic Rhinitis and its Impact on Asthma (ARIA) working group classify the severity of allergic rhinitis as "mild" or "moderate/severe" depending on the severity of symptoms and quality of life outcomes.[3,7,42] Therefore, treatment of allergic rhinitis in children and adolescents focuses on achieving patients' wellbeing by minimizing symptoms and improving physical, psychological and social functioning.[3,7,42] For this reason, health-related quality-of-life is recognized as a relevant instrument for achieving a complete picture of a child's health status.[33-34,104-107]

The impact of allergic rhinitis on quality of life can be assessed by the child itself by means of several validated instruments.[108-111] Health-related quality of life questionnaires are developed for children and adolescents with allergic rhinitis. These questionnaires have good measurement properties and validity, and can be completed reliably and accurately by children (age > 6 year) themselves.[32,108] The questionnaires can be used both

in clinical trials and in clinical practice to assess the impact of allergic rhinitis on a child's life, to determine the burden of the disease, and the effect of treatment. The importance of allergic rhinitis and its impact on health-related quality of life is confirmed by the international guidelines for respiratory allergy. Both the Global Initiative for Asthma (GINA) and the ARIA documents consider health- related quality of life as a relevant issue for the choice of appropriate treatment. It has also become increasingly important in health care research; assessment of the impact of the disease and its treatment on patients' quality of life provides a more comprehensive approach in outcome evaluation.[104,112,113]

FRACTION EXHALED NITRIC OXIDE

Allergic rhinitis and asthma very often coexist in the same patients as common, chronic diseases of the respiratory tract. Both conditions often show systemic manifestations including airway inflammation and blood eosinophilia.[3,7,42] This airway inflammation is responsible for narrowing of the airways which worsens symptoms such as shortness of breath, cough, and wheeze.[3,7,42] Airway inflammation in asthma and allergic rhinitis involves release of biomarkers including nitric oxide (NO).[114,115] NO production has been shown to increase when there is eosinophilic airway inflammation.[114,115] The presence of endogenous NO in exhaled air was first reported in 1991 by Gustafsson et al.[116] In 1993 Alving et al. found that NO in exhaled air was elevated in patients with asthma.[117] In continuation of this study by Alving et al. much research has been done to elucidate the role of NO in airway inflammation. Nowadays, the measurement of fractional exhaled nitric oxide (FeNO) could be considered as a reliable, noninvasive marker of airway inflammation and is well adapted for use in children.[118-120] Measurement of exhaled nitric oxide (eNO) is frequently used to monitor airway inflammation in asthma.[115,121,122]

Asthma and allergic rhinitis have common risk factors and are often associated.[3,7,42] The pathophysiological relation between upper and lower airways is based on similarities in their mucosal histology.[123-125] Airway inflammation appears to be the most important cause of increased FeNO.[108] In both conditions, the increase of FeNO suggests a close association between upper and lower airways, and a relationship has been shown between eNO, asthma and atopy. Studies on FeNO have shown elevated levels in, for example, patients with atopic asthma, allergic rhinitis or atopic eczema.[126-130]

Allergic rhinitis and FeNO: relationship with quality of life

There is increasing evidence that the degree of airway inflammation correlates with the quality of life of patients with asthma and allergic rhinitis.[131,132] For example, Robberts et al. showed a significant correlation between NO levels and the Paediatric Allergic Quality of Life Questionnaire scores in children with grass pollen induced allergic rhinitis

(r=0.41).[131] Another study by Cerović et al. found a significant correlation between NO values and Pediatric Asthma Quality of Life Questionnaire scores in children suffering from bronchial asthma.[132] This relationship between patients' well-being, as measured by the questionnaires, and both upper and lower airway complaints or airway inflammation has not been previously examined in children with a house dust mite induced allergic rhinitis. Monitoring exhaled NO and the well-being of the patient could be of value in airway disease management.

MONOSENSITIZATION AND POLYSENSITIZATION

Some atopic children are sensitized to only one allergen (monosensitization) while others show sensitization to more than one allergen in screening tests of allergy (polysensitization).[133] Polysensitization might be a phenomenon that is clinically relevant. Several studies have pointed out that up to 90% of patients are polysensitized.[134-136] Only few studies have addressed polysensitization in children.[133,136] Assessment of allergic sensitization is considered to be important in the diagnosis and management of allergic disease throughout childhood.[137] Persisting or recurrent possible allergic symptoms can occur in both allergic and non-allergic disorders, and this overlap can confound the diagnosis and therapy. Allergy testing could be useful for the early identification of infants at increased risk for later development of allergic diseases, specific allergy treatment, specific allergen avoidance measures, and relevant pharmacotherapy.[137]

Polysensitization is significantly associated with impaired quality of life[138], a phenomenon that is quite frequent and that may influence the attitude of physicians in managing allergic patients, including the prescription of specific immunotherapy.[135]

AIM OF THE THESIS

The main objective of this thesis is to assess the effectiveness of sublingual immunotherapy in children and adolescents with a proven house dust mite induced allergic rhinitis in general practice.

Outline of the thesis

Chapter 2 describes the incidence and management of allergic rhinitis in children in general practice. Incidence rates are stratified for several socio-demographic characteristics. Results from nationwide studies (performed in 1987 and 2001) are compared. The aim of **Chapter 3** is to examine the quality of available systematic reviews and meta-analyses of sublingual immunotherapy for allergic rhinitis in children, published since

2000 using the AMSTAR instrument. **Chapter 4** gives an overview of the study design of the randomized double-blind placebo-controlled trial that we performed to study the effect of sublingual immunotherapy in children from primary care with a proven house dust mite induced allergic rhinitis; recruitment characteristics are also described. The results and conclusions of the trial are presented in **Chapter 5**. In **Chapter 6** the focus is on the associations between fractional exhaled nitric oxide, upper and lower airway complaints, and quality of life in children with allergic rhinitis. **Chapter 7** describes the pattern of sensitization to common allergens and the association with age, gender and clinical symptoms in children in primary care who are diagnosed with allergic rhinitis. **Chapter 8** discusses the main findings of the previous chapters, provides implications for practice, and presents suggestions for future directions of research for sublingual immunotherapy in children.

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Chapter 2

Allergic rhinitis in children: incidence and treatment in Dutch general practice in 1987 and 2001

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ABSTRACT

Background

Allergic rhinitis is a common chronic disorder in children, mostly diagnosed in primary health care. This study investigated the national incidence and treatment of allergic rhinitis among children aged 0-17 years in Dutch general practice in 1987 and 2001 to establish whether changes have occurred.

Methods

A comparison was made with data from the first (1987) and second (2001) Dutch national surveys of general practice on children aged 0-17 years. Incidence rates were compared by age, sex, level of urbanization and season. The management of the general practitioner was assessed regarding drug prescriptions and referrals to medical specialists, and compared with the clinical guideline issued in 1996.

Results

The incidence rate of allergic rhinitis increased from 6.6 (1987) to 9.2 (2001) per 1000 person-years. We found a male predominance with a switch in adolescence to a female predominance at both time points. The increase in incidence was the highest in rural (<30,000 inhabitants) and suburban areas (30,000-50,000 inhabitants). Compared to 1987, there was a significant increase in incidence in the central part of the Netherlands in 2001. In both years, the incidence was higher in spring compared with the other seasons. In 2001, children of natives and western immigrants visited the general practitioner more often with complaints of allergic rhinitis compared to 1987. In 1987 prescribed medication consisted mainly of nasal corticosteroids (36%) and in 2001 of oral antihistamines (45%). Although a clinical guideline was not issued until 1996, overall, the treatment of allergic rhinitis by general practitioners was in both years in accordance with the current clinical guideline, but with a stronger adherence in 2001.

Conclusion

The results show an increased incidence in the past decades of allergic rhinitis in children in Dutch general practice. The shift to a smaller spectrum of prescriptions in 2001 may be a result of the 1996 clinical guideline.

BACKGROUND

Allergic rhinitis is a common chronic disorder among children and its prevalence has increased throughout Europe over the past five decades.[1-4] For example in Scottish children over a 25 year period the prevalence rose from 3% in 1964 to 12% in 1989.[1] Among Swedish schoolchildren the prevalence of allergic rhinitis, asthma/wheeze or eczema increased continuously from 24% to 33% between 1979 and 1991 and in Danish children rhinitis increased steadily from 1986 to 2001 (12%-23%).[2,3] Some studies reported that many environmental factors, such as a western lifestyle, the "hygiene hypothesis" and air pollution, may contribute to the increasing asthma and atopy rates.[5-7]

Allergic rhinitis is characterized by nasal obstruction, sneezing, itching of the nose and/or postnasal drainage, and is often associated with respiratory and ocular symptoms.[8,9] Previously, allergic rhinitis has been subdivided, into seasonal and perennial allergic rhinitis. In 1999, the World Health Organisation introduced a new classification of subdividing allergic rhinitis into intermittent allergic rhinitis and persistent allergic rhinitis (ARIA Guidelines), instead of the traditional seasonal and perennial divisions.[10]

Symptoms of allergic rhinitis can seriously affect the quality of daily life of children in terms of physical and psychological well-being.[9,11,12] Therefore, an adequate management of allergic rhinitis may be an important component in improving the quality of life. Also, an adequate management for co-morbid conditions or complicating respiratory conditions such as asthma, eczema, sinusitis, recurrent middle-ear infections and sleep disorders may be of great importance.[8] The direct costs of treating allergic rhinitis and indirect costs (loss of productivity, absence from school resulting from allergic rhinitis) are substantial.[13-15]

Allergic rhinitis develops before the age of 20 years in 80% of all patients with allergic rhinitis.[8] Allergic rhinitis is also the most prevalent allergic disorder in children and is mostly diagnosed in primary health care.[16] In recent years, national and international guidelines have been developed to enhance the effectiveness and quality of management of patients with allergic rhinitis.[17] In 1996 a guideline on allergic rhinitis was issued by the Dutch College of General Practitioners (NHG); this Practice Guideline was updated in May 2006.[18,19] Knowledge about the incidence and management of allergic rhinitis might improve the care of allergic rhinitis among general practitioners (GP) and may contribute to wider improvements in health and healthcare services and interventions.

Here, we report on the incidence and management of allergic rhinitis in children in Dutch general practice. The research questions were:

- What is the incidence of allergic rhinitis in children aged 0-17 years related to age, gender, season, region and urbanization, and did it change between 1987 and 2001?
- What is the treatment of allergic rhinitis by GPs, and did this change between 1987 and 2001?

METHODS

Data were analysed from the first and second Dutch National surveys of general practice, which were performed by the Netherlands Institute for Health Services Research (NIVEL) in 1987 and 2001.[20,21] Each survey included a representative sample of the Dutch population. In the Netherlands, general practices have a fixed list size, all non-institutionalised inhabitants are listed in a general practice, and GPs have a gate-keeping role. Usually, the first contact with health care, in a broad sense, is the contact with the GP. For the current study, data from both surveys for children aged 0-17 years were analysed. The participating GPs were representative for age and gender of all Dutch GPs.

First Dutch National survey 1987

A sample of 161 GPs in 103 practices was randomly selected to participate in the survey. The GPs were divided into four groups, and each group recorded data on registration forms about all contacts between patient and practice during one of four consecutive 3-month periods during 1987. The four registration periods covered one calendar year to correct for seasonal variability of morbidity. Other socio-demographic characteristics (such as ethnicity) were obtained by a questionnaire and filled out by parents, or by the children themselves if they were older than 12 years (response rate 91.2%). Data recorded from each consultation included patient characteristics (age, gender), diagnosis, prescription of drugs, and referrals. Specially trained workers used the International Classification of Primary Care (ICPC) to code the diagnoses made by the GP. Prescribed medication was automatically coded using the Anatomical Therapeutic Chemical (ATC) coding system.[20]

Second Dutch National survey 2001

The second national survey was carried out in 2001. Data on all physician–patient contacts during 12 months were extracted from electronic medical records in 104 practices with 195 GPs. The GPs registered all health problems presented within one consultation and coded diagnoses using the ICPC. Also, all drug prescriptions (coded according to relevant ATC classification) and referrals made by the GP were extracted. Patient characteristics such as age and gender were derived from the GPs' computerized patient files. As in 1987, data on ethnicity were obtained by a questionnaire (response rate 76%). For the current analysis, data from 9 of the 104 practices (10 GPs) were excluded for the following reasons: five practices with inadequate registration of patient contacts or drug prescription were excluded after quality control, 4 other practices were excluded because of software problems.[21]

Episodes of disease

Both surveys were episode oriented, meaning that a consultation on a new health problem marked the beginning of a new episode. If there were multiple consultations in a single episode, chronologically the last diagnosis made was considered the diagnosis of the episode.

To identify the episodes for allergic rhinitis we selected all episodes coded with ICPC code R97: Hay Fever/Allergic rhinitis. Medication was selected using the ATC codes. The ATC codes of interest were R06A (antihistamines for systemic use), R01A (decongestants and other nasal preparations for topical use, i.e. nasal steroids) and S01G (ophthalmologic decongestants and anti allergics).

The management of the GP was assessed regarding drug prescriptions and referrals to medical specialists and compared with the clinical guideline issued in 1996.[18]

Both surveys provided the opportunity to determine the incidence and management of allergic rhinitis according to age, gender, region, season and urbanization. For age, children were divided in subgroups of age 0-4, 5-9,10-14 and 15-17 years. Urbanization was categorized into four categories based on the size of the municipality: <30,000 inhabitants (rural areas), 30,000-50,000 inhabitants (suburban areas), > 50,000 inhabitants (urban areas) and "large cities" (Amsterdam, Rotterdam and The Hague). The Netherlands was divided into a Northern, Central and Southern region. Season was divided in spring (April-June), summer (July-September), autumn (October-December) and winter (January-March). Ethnicity was derived from the country of birth of the parents. If either parent was born in Turkey, Africa, Asia (except Japan and Indonesia) and Central or South America, their children were considered to be children of non-western origin (in accordance with the classification of Statistics Netherlands). All other children were defined as western. Hence, children of western origin included children from the native population and children from parents born in other western countries.[20,21]

Ethical approval

The surveys were carried out according to Dutch legislation on privacy in 1987 and in 2001. The privacy regulation of the second survey was approved by the Dutch Data Protection Authority. According to Dutch legislation, obtaining informed consent is not obligatory for observational studies.

STATISTICAL ANALYSES

We defined incidence as the number of new episodes of allergic rhinitis per 1000 person years. Statistical analyses were performed using SPSS 11 and Stata 8.0 SE. The 95% confidence intervals (CI) were calculated assuming a Poisson distribution.

We calculated the incidence rate by dividing the total number of new episodes (numerator) by the study population at risk multiplied by the follow-up time (denominator). In 1987 the denominator was calculated by multiplying the number of all patients listed in the participating practices by the follow-up time (person years). In 2001, persons that moved into or out of the participating practices during the registration period were assumed to contribute for half a year to the follow-up time. The so-called mid-time population was calculated as the mean of all listed patients (aged 0-17 years) of all participating GPs, at the beginning and at the end of the registration period. Data were stratified for age categories, gender, urbanization level, region, season and ethnicity.

RESULTS

Study populations in 1987 and 2001

In 1987 86,577 children aged 0-17 years participated and in 2001 81,716 children aged 0-17 years participated. In these groups, 143 first contacts of allergic rhinitis occurred in 1987(during 4 consecutive 3-month periods) and 753 in 2001 (during 12 months). These first contacts formed the basis for our calculation of the incidence rates for allergic rhinitis.

Incidence

The incidence of allergic rhinitis in children in 1987 was 6.6 (CI: 5.6 – 7.8) per 1000 person years. In 2001 the incidence increased to 9.2 (CI: 8.5 – 9.9) per 1000 person years, i.e. a significant increase of 39% compared to 1987.

The incidence by age and gender is presented in Figures 2.1 and 2.2 and Table 2.1. Table 2.1 shows that the peak age group of allergic rhinitis was 15-17 years in both surveys. In 2001, the incidence rate of allergic rhinitis in younger children (5-9 years) is almost double compared to 1987 ($p=0.002$). In 2001, the age group 10-14 years also presented allergic rhinitis more frequently to the GP than in 1987 ($p= 0.003$). Comparing Figures 2.1 and 2.2 shows that girls have a steeper increase in incidence of allergic rhinitis by age, accelerating after the age of 14 years.

In 2001, the incidence rate of allergic rhinitis increased significantly in rural areas (<30,000 inhabitants) and suburban areas (30,000 – 50,000 inhabitants), compared to 1987 ($p<0.001$ and $p=0.019$, respectively). The incidence rates in other urbanization levels remained stable in both surveys (Table 2.1). In 1987, there was a significantly lower incidence rate in rural areas compared to other urbanization levels ($p=0.05$), whereas in 2001,there was a significantly lower incidence rate in large cities compared to other urbanization levels ($p=0.05$).

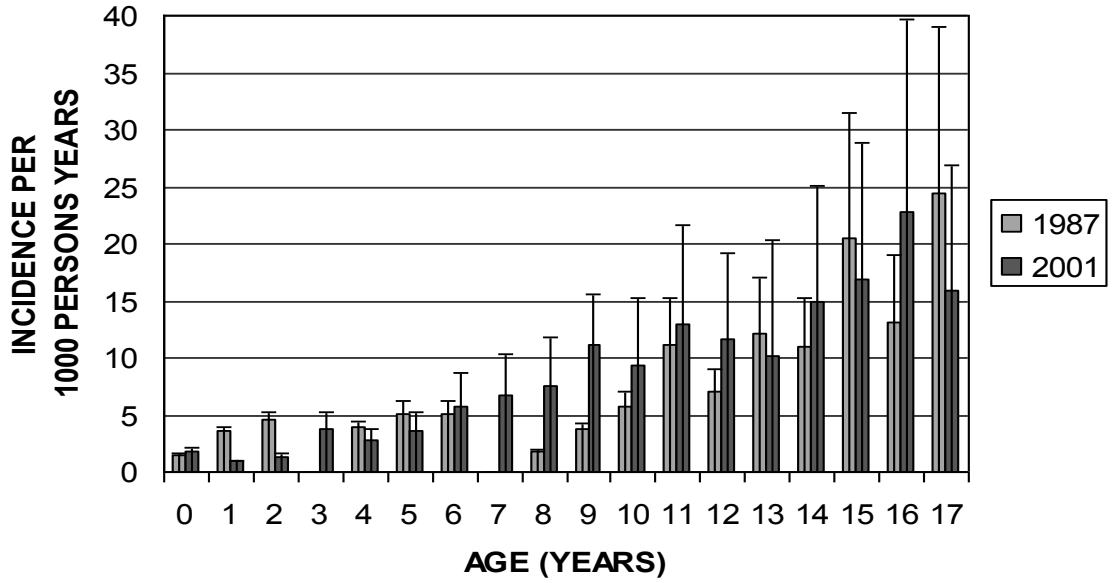

Figure 2.1: Incidence rate of allergic rhinitis in girls in 1987 and 2001 by age per 1000 person years

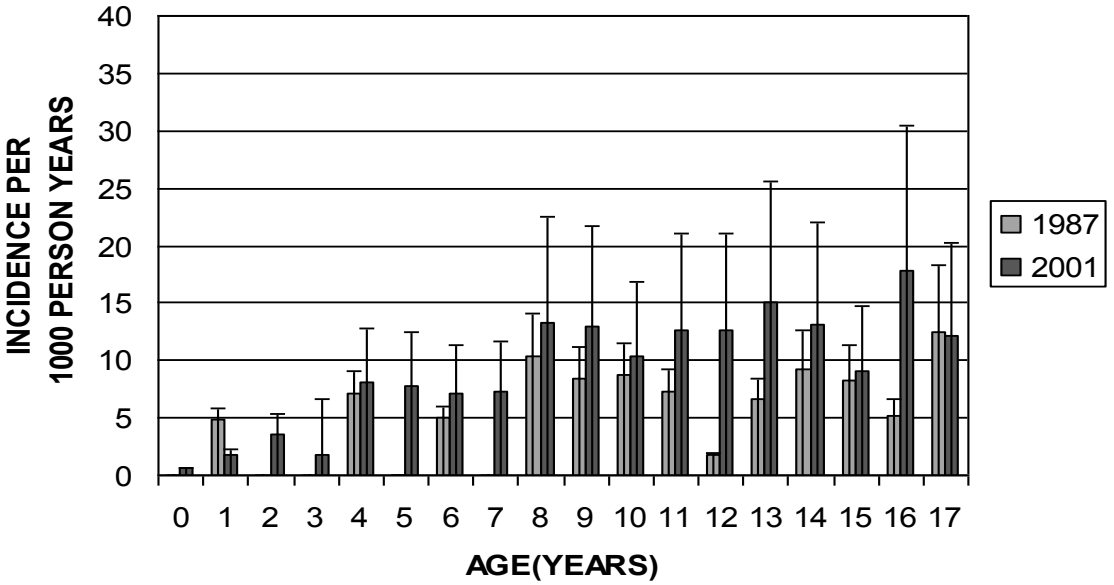

Figure 2.2: Incidence of allergic rhinitis in boys in 1987 and 2001 by age per 1000 person years

Allergic rhinitis was more frequent in the central part of the Netherlands in 2001 compared to 1987 ($p<0.001$). In both surveys, we found the highest incidence rate in the southern part, although the differences were not significant. There was a peak incidence in spring in both surveys; in 2001 the spring incidence rate of allergic rhinitis was more than doubled compared with 1987.

Table 2.1: Incidence rate and 95% confidence interval of allergic rhinitis in children aged 0-17 years, by age group, urbanization level, region and season in 1987 and 2001; per 1000 person years

	1987		2001		
	Incidence per 1000 person years		Incidence per 1000 person years		
	0-17 years	95% CI	0-17 years	95% CI	P-value
Age Categories					
0-4 years	2.9	1.5-5.0	2.7	2.1-3.5	0.817
5-9 years	4.8	3.1-7.2	8.4	7.3-9.7	0.002
10-14 years	8.1	6.0-10.9	12.2	10.9-13.8	0.003
15-17 years	13.5	10.3-17.66	15.8	13.7-18.0	0.282
Urbanization level					
< 30 000 inhabitants	5.1	3.6-6.9	9.0	8.1-10.1	<0.001
30 000-50 000 inhabitants	7.0	5.3-9.1	9.9	8.4-11.6	0.019
> 50 000 inhabitants	8.5	6.0-11.7	9.7	8.6-11.0	0.407
Large cities *	7.3	4.0-12.7	6.0	4.1-8.4	0.549
Region					
North	5.3	2.8-9.1	7.7	6.2-9.5	0.157
Mid	6.4	5.1-7.9	9.4	8.6-10.3	0.001
South	7.7	5.5-10.5	9.5	8.3-9.9	0.186
Season					
Winter	4.6	2.9-6.9	4.8	3.9-5.9	0.826
Spring	9.4	7.2-12.1	22.7	20.7-24.9	<0.001
Summer	7.7	5.3-10.7	5.2	4.3-6.3	0.077
Autumn	4.5	3.0-6.5	4.3	3.4-5.3	0.834
Ethnicity					
Natives & Western Immigrants	6.4	5.2-7.8	9.7	8.9-10.6	<0.001
Non-Western Immigrants	9.1	4.6-16.3	10.5	8.0-13.5	0.652
Missing ethnicity	6.6	4.1-8.2	7.7	6.7-9.0	0.111
Total	6.6	5.6-7.8	9.2	8.5-9.9	<0.001

In 2001 western children (natives and western immigrants) visited the GP more often with complaints of allergic rhinitis, compared to 1987 (p=0.001).

Prescriptions

Table 2.2 shows medication prescriptions during the first contact for an allergic rhinitis episode. Table 2.3 presents the type of prescribed medication for allergic rhinitis in the first contact. In 1987 the GPs issued 137 prescriptions in the first contact. In 1987, a prescription was written in 77.6% of all first consultations and in most cases (62.7% of all cases) the GP prescribed only one drug. In 2001 the GPs made 669 prescriptions in the

first contact for the first episode. In 68.5% of the episodes the GP prescribed medication in the first contact; in 50.9% of these first episodes only one drug was prescribed.

In both surveys the majority of children was treated with decongestants or other nasal preparations (R01A) and antihistamines (R06A), which is in accordance with the 1996 clinical guideline. From 1987 to 2001 prescriptions for antihistamines (R06A) rose from 23% to 45%. The number of prescriptions for drugs for nasal symptoms (R01A) remained stable over the last 15 years, whereas prescriptions for anti-inflammatory eye drops (S01G) increased from 7% to 13%. The prescriptions in 1987 showed a wider variety of medication type shifting in 2001 to a smaller spectrum.

Table 2.2: Number and percentage of prescriptions during first contact of allergic rhinitis episode in 1987 and 2001

	1987		2001	
Total number of episodes	143	100%	753	100%
No prescription	32	22.4%	237	31.5%
1 prescription	89	62.7%	383	50.8%
2 prescriptions	18	12.7%	115	15.3%
3 prescriptions	4	2.8%	18	2.4%

Table 2.3: Prescribed medication in the first contact from an episode of allergic rhinitis in 1987 and 2001

	1987		2001	
Total prescriptions in the first contact of episode	137	100%	669	100%
R06A antihistamines for systemic use	32	23.3%	303	45.3%
R01A decongestants and other nasal preparations for topical use	49	35.8%	240	35.9%
S01G decongestants and antiallergics	10	7.3%	89	13.3%
J01A tetracyclines	2	1.5%	0	0%
J01C beta-lactam antibacterials, penicillins	3	2.2%	0	0%
J03B anti infectives for systemic use	2	1.5%	0	0%
R03A adrenergics, inhalants	2	1.5%	9	1.4%
R03B other drugs for obstructive airway diseases, inhalants	3	2.2%	2	0.3%
R03C adrenergics for systemic use	3	2.2%	2	0.3%
R05C expectorants, excl. combinations with cough suppressants	3	2.2%	1	0.1%
S03C corticosteroids and anti infectives in combination	4	2.8%	0	0%
V01A allergens	3	2.2%	0	0%
Other (D07A corticosteroids plain, S01B Anti-inflammator agents)	21	15.3%	23	3.4%

Referral to medical specialists

Relatively few children were referred to a medical specialist. In 1987 only 4 out of 143 children (1.4%), and in 2001, 4 out of 753 children (0.5%) were referred to hospital for the diagnosis allergic rhinitis. In both surveys most children were referred to ENT specialists.

DISCUSSION

The results of this study show that the incidence of allergic rhinitis in children in general practice in the Netherlands has increased by almost 40% between 1987 and 2001. This increase is in accordance with previous studies showing an increase ranging from 40% to almost 400% in the general population worldwide.[1-4] The huge increases were found in the periods from 1964-1989[1] and in 1979-1991.[2] More recent studies [3,22] demonstrate a less extreme increase and it is evenly suggested that the prevalence of allergic rhinitis may be stabilizing over the recent decades.[22]

Our results may be considered representative for all children treated in primary care in the Netherlands. Although childhood consultation rates in general practice have decreased over the past 15 years, respiratory problems are still the most frequently presented health problem in children.[23] In recent years advertisements have increasingly targeted allergy medication, which are available without prescription (over-the-counter drugs), which could have reduced the consultation behaviour of parents and children. This could indicate that the incidence of allergic rhinitis in the population is even higher.

In both surveys we found that more boys were affected than girls. However, after adolescence a switch is found to females, who are affected slightly more than males. In childhood, allergic rhinitis is more common in boys than in girls.[8,9] The increase in the incidence rates among girls in adolescence may be explained by a change of interpretation of complaints and visiting the GP for those complaints. In adolescence, girls are more likely to overestimate the severity of the disease whereas boys tend to underestimate.[24-27] The gender differences and age-related differences, which we observed may also be related to differences in the hormonal environment.[28]

In 2001, we found a significant increase in the incidence of allergic rhinitis in rural (<30,000 inhabitants) and suburban areas (30,000- 50,000 inhabitants) compared to 1987, which is in accordance with previous studies.[29,30] However, rural living has been associated with a lower prevalence of atopy and allergic rhinitis in both children and adults.[29,31] An explanation for this discrepancy can be that environmental changes affect the whole society, which promotes an increase in allergic rhinitis in both rural and urban environments.[29] In 2001, we found a significant unexplained lower incidence rate in large cities compared to other urbanization levels in 2001.

In both surveys the incidence was the highest in spring, meaning that most visits to the GP for hay fever are as expected in spring.[8,9] Although most visits were in spring, the visits for complaints of allergic rhinitis in summer, autumn and winter were substantial in both surveys. Allergic rhinitis in spring may represent intermittent (previously called 'seasonal') as well as persistent rhinitis.

GP management

The management of allergic rhinitis consists of a pharmacological therapy and a non-pharmacological therapy, such as allergen avoidance advice.[18] Although a clinical guideline was not issued until 1996, the treatment of allergic rhinitis by GPs in 1987 was more or less in accordance with the guideline. The prescriptions in 1987 showed a wider variety of medication type and shifted in 2001 to a smaller spectrum; this could be a result of the 1996 clinical guideline.[18] In 2001, the participating GPs treated allergic rhinitis in children according to the 1996 clinical guideline for general practice. Relatively few children were referred to a medical specialist.

Limitations of this study

There were small differences in the design of the two national surveys, which might hinder comparability of the data. Some of the differences in occurrence may be explained by the fact that ICPC coding was not performed the same in both surveys: in 1987 clerks coded diagnoses afterwards by hand, whereas in 2001 the GPs coded the diagnoses themselves during the consultation in a computerized patient file. This might result in differences concerning the incidence rate of AR. Some cases of AR might be missed when clerks recode doctor's diagnosis afterwards, resulting in an unintentional lower incidence rate in 1987. Furthermore, we have no information on non-pharmacological treatment, such as advice.

CONCLUSION

The incidence of allergic rhinitis among children in general practice in the Netherlands has increased by almost 40% over the past 15 years. The shift to a smaller spectrum of prescriptions in 2001 may be a result of the 1996 clinical guideline.

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Chapter 3

Sublingual immunotherapy in children with allergic rhinitis: quality of systematic reviews

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ABSTRACT

Systematic reviews have gained popularity as a way to combine the increasing amount of research information. This study assessed the quality of systematic reviews and meta-analyses of sublingual immunotherapy for allergic rhinitis in children, published since 2000. Eligible reviews were identified by searching Medline/Pubmed, Embase and the Cochrane Library, from 2000 through 2008. Methodological quality was assessed with the AMSTAR instrument. Ten systematic reviews were included, one of which was published in the Cochrane Library. Eight reviews gave some details about the search strategy. None of the reviews included measures to avoid selection bias. In 60% of the reviews the methodological quality of the included studies was (partly) assessed. Four reviews pooled results of individual studies, neglecting clinical heterogeneity. Three of the 10 reviews provided information about sources of funding, or grants from industry. Of the 10 reviews, the 6 reviews with the highest overall score scored 5-8 points, indicating moderate quality. Systematic reviews are useful to evaluate the efficacy of sublingual immunotherapy in children. Although more reviews have become available, the methodological quality could be improved. Sublingual immunotherapy for children could be promising, but methodological flaws in the reviews and individual studies are too serious to draw definite conclusions.

BACKGROUND

Allergic rhinitis is a highly prevalent chronic disease in children and adults which, despite optimal treatment, can adversely affect quality of life.[1,2] Allergen immunotherapy can significantly reduce symptoms and medication use, prevent new sensitizations and, possibly, even the onset of asthma.[3-8] The use of subcutaneous immunotherapy (SCIT), with uncomfortable injections, in children and adults is limited because of the risk of severe side effects.[9] Therefore, alternative routes for the delivery of allergens have been developed.

The sublingual immunotherapy (SLIT) route, consisting of drops and fast-dissolving tablets, is the most interesting and has become widely accepted in the past decade.[10-12] There are several systematic reviews and meta-analyses on the efficacy of SLIT in children, but their conclusions are contradictory. For example, some concluded that there was insufficient evidence to recommend SLIT for use in routine clinical practice[13,14], whereas others reported that SLIT is effective in the treatment of allergic disease in children.[15,16]

A systematic review can be defined as using an objective and transparent approach to find and synthesize published research with the aim to minimise bias, and a meta-analysis as a systematic review which uses quantitative methods to combine the results of individual studies.[17,18] Both types of review will provide evidence-based medicine, that involves tracing the best available evidence with which to answer clinical questions. Systematic reviews and meta-analyses have gained popularity as a way of combining the increasing amount of research information.[19]

Systematic reviews and meta-analyses reporting the findings on SLIT in children can vary greatly in quality, and have not been comprehensively appraised with respect to their methodological quality.

Rather than focusing on the content of the reviews, this review aims to identify and assess the methodological quality of the available systematic reviews and meta-analyses of SLIT (published since 2000) for allergic rhinitis in children.

METHODS

Literature search and review selection

Literature searches were conducted in PubMed, Embase and the Cochrane Library, identifying reviews or meta-analyses published between 1 January 2000 and 31 December 2008. The full search strategies can be found in Appendix I. Additional articles were identified by manually searching references from the retrieved articles and the authors' own literature database. As the first phase of screening, two reviewers (CdB and JvdW) independently examined the titles and abstracts of the search results. The second phase

of screening was based on full-text articles, which were obtained and assessed for inclusion with the predetermined selection criteria. The data from all reviews that met the selection criteria were also extracted independently by two reviewers (CdB and JvdW). Disagreements, if any, were resolved by discussion.

Inclusion criteria

The eligibility criteria for including systematic reviews and meta-analyses for step one were:

- "Systematic review" or "meta-analysis" in title or abstract and/or
- Literature searches described (databases, period, search terms, such as "immunotherapy", " allergic rhinitis", "children")

After this first step the additional eligibility criteria were:

- Reviews including randomized controlled trials (RCTs), performed in pediatric populations or in both adult and pediatric populations, assessing sublingual immunotherapy for allergic rhinitis

Quality of the included reviews

Methodological quality was assessed with the measurement tool 'assessment of multiple systematic reviews' (AMSTAR).[20-22] The tool consists of 11 items and has good face and content validity for measuring the methodological quality of systematic reviews (see Appendix II). Two reviewers (CdB and JvdW) independently filled in a checklist with for every item, detailed instructions for assessing the quality of the included studies. Each question had four possible responses: "yes," "no," "can't answer" and "not applicable." A "yes" gave a score of 1; any other response resulted in a score of 0. We summed the number of items that were scored positively. The maximum score on AMSTAR is 11; scores of 0-4 indicate that the review is of low quality, 5-8 of moderate quality, and 9-11 of high quality.[20-23] In order to adjust for the number of non-applicable items, we also calculated the proportion of items scored positively divided by the total number of applicable items.

Reviews: data extraction

Data were extracted on general characteristics (publication year, source, source of funding), clinical issues (population, definition of allergic rhinitis, intervention), and methodological characteristics (design, methodological quality).

None of the authors who did the inclusion, extracted the data and assessed the quality of the systematic reviews (CdB and JvdW), were co-authors of any of the included reviews.

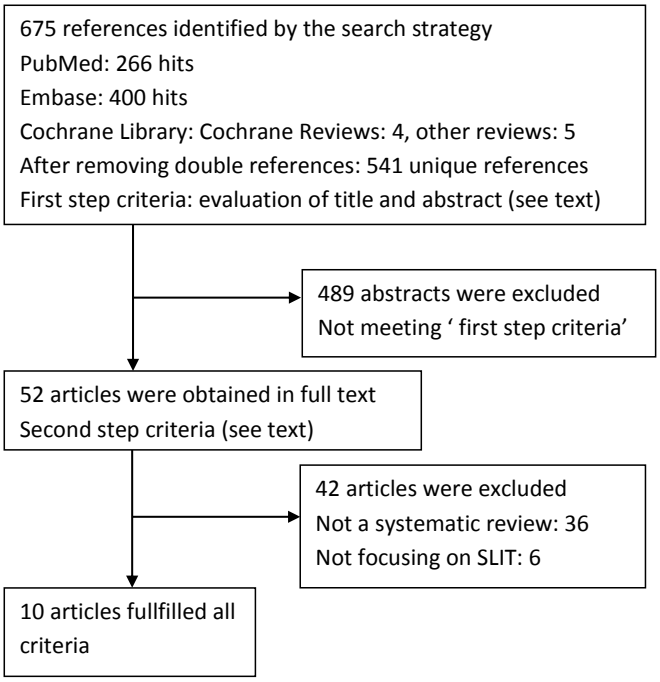

Figure 3.1: Flow chart of the literature search and selection

Analysis

The analysis of the data was descriptive.

RESULTS

Identification of reviews

Our primary search resulted in 541 publications (Figure 3.1). After reading the abstracts, 52 full-text articles were selected and read (step 2). Most of the excluded articles did not meet the criteria of being a systematic review. The reviews that were excluded in the last phase can be found in the orginal article. Finally, we identified 10 reviews that met the inclusion criteria.[13,16,24-31] One was a Cochrane review, which was also published as a journal article two years later.[13,31]

In the reviews, the number of included studies ranged from 8 to 46. Most of the reviews included only RCTs, and one review gave an overview of other reviews published earlier.[24] Table 3.1 presents the characteristics of the reviews. The number of published reviews increased from one in 2003, to three in 2008.

Table 3.1: Characteristics of the reviews

First author	Year published	Participants**	Disease*	Type of immunotherapy a	Search period	Number of slit studies included
Wilson	2003	Children, adults	AR Asthma	SLIT	1966-2002	22
Sopo	2004	Pediatric 0-18 years	AR Asthma	SLIT	?-2003	8
Olaguibel	2005	Pediatric <14 years	Rhinitis Asthma	SLIT	?-2004	7
Wilson	2005	Children, adults	AR Asthma	SLIT	1966-2002	22
Penagos	2006	Pediatric 0-18 years	AR Asthma	SLIT	1966-2006	10
Cox	2007	Pediatrics< 18 years	AR	SLIT	2005-2007	19
Hoeks	2007	Children	AR Asthma	SLIT	1996-2007	13
Calderon	2008	Adults, pediatric	AR	SLIT SCIT	?-2007	46
Larenas-Linnemann	2008	Pediatric <14 years	AR Asthma	SLIT SCIT	1993-2008	13
Röder	2008	Pediatric 0-18 years	AR	SCIT SLIT LNIT OIT	1966-2006	11

AR= allergic rhinitis

a: SLIT= sublingual immunotherapy; SCIT= subcutaneous immunotherap; LNIT= Local nasal immunotherapy; OIT=Oral Immunotherapy

* included in the search strategy

** as described in the article

Review characteristics

Table 3.2 summarizes the characteristics of the included studies regarding intervention, participants and outcomes. Nine reviews reported on characteristics of the included studies regarding intervention, such as the number of patients who received placebo or active treatment, dosage of SLIT, and duration of the study. Eight reviews reported characteristics of the participants in the studies; this varied from reporting only the population in the studies to describing gender, age, country and dropout rates. Seven reviews described the characteristics of the outcomes of the included studies (ranging from 1 to 6 items); the main characteristics were AR/nasal symptom score and rescue medication. One review reported no details on intervention, participants or outcomes of the included studies.[27]

Table 3.3 shows the results of the data extraction of the review process of the systematic reviews with regard to the databases used, the list of included/excluded studies, and year of publication. Four reviews used 4 databases to search for literature.[13,16,28,31] All reviews searched in Pubmed/Medline, followed by Embase, and the Cochrane Library in 6 reviews. Only one review reported a list of included and excluded studies.[13] In 60% of the reviews only a list of the included studies was reported.[16,26,28-31]

Table 3.2: Study characteristics as reported in the review

	Wilson 2003	Sopo 2004	Olaguibel 2005	Wilson 2005	Penagos 2006	Cox 2007	Hoeks 2007	Larenas-Linneman 2008	Calderon 2008	Röder 2008
INTERVENTION										
Duration	x	x	x	x	x		x		x	x
Dosage		x	x		x	x	x		x	x
No of placebo/verum	x		x	x	x	x	x		x	x
Type of allergen	x	x	x	x	x	x	x		x	x
TOTAL	3	3	4	3	4	3	4	0	4	4
PARTICIPANTS										
Population	x			x						
Gender	x	x				x				x
Age		x			x		x			x
Country		x								
Conditions reported										
• Asthma (A)		x			x	x	x		x	x
• Rhinitis (R)		x			x	x	x		x	x
• Conjunctivitis (C)		x			x		x		x	
Drop outs					x				x	x
TOTAL	2	6	0	1	5	3	4	0	4	5
OUTCOMES										
AR/nasal symptom score	x			x	x		x			x
Conjunctival	x									x
Rescue medication	x			x	x		x			x
(Total/specfic) IgE/Ig	x						x			
Skin prick test	x						x			
Lung function tests							x			
Nasal provocation	x									
Conjuctivitis provocation test							x			
Side effects			x			x				
TOTAL	6	0	1	2	2	1	6	0	0	3

Table 3.3: Review characteristics

Databases used	
PubMed/Medline	10
EMBASE	7
Cochrane Library	7
Other (i.e. ISI, CINAHL, Scisearch)	4
Number of databases used	
1	2
2	1
3	3
4	4
List of included and excluded studies	
Neither included nor excluded studies listed	3
Only included studies	6
Both included and excluded studies listed	1

Methodological quality

Table 3.4 summarizes the components of the AMSTAR for the selected reviews. Only two reviews (the Cochrane review and the journal article based on it) provided details about their design before conducting the review as the protocol for these reviews was already published.[13,31] Other reviews did not report an a priori design. Of the 10 reviews, 5 did not report duplicate study selection and data extraction. Two reviews had only one author; thus we assumed that no duplicate study selection and data extraction took place. In 8 of the reviews the authors provided some details about their search strategy. This varied from providing only keywords to reporting the full search strategy, including MeSH terms and text words. The search strategies were often limited, e.g. only a few synonyms were used. In about 50% of cases the authors also searched for 'grey' literature. Only one review reported a complete list of the included and excluded studies.[13]

In 6 of the reviews the methodological quality of the included studies was (partially) assessed by the authors and (some of) the results were evaluated. Different methods were used. For example, Röder et al. used the Delphi list[32], Penagos et al. and Hoeks et al. used the Jadad scale [33,34], the review of Wilson et al. assessed methodological quality according to the guidelines of the Cochrane Collaboration [35], and Sopo et al. used criteria provided by the Evidence-Based Medicine Working Group.[36] Only 4 of the 10 reviews used the results of the methodological quality for the analysis in the Conclusions section of the review.[16,26,29,30]

For combining the findings of studies, four reviews assessed the homogeneity with the Chi-square test for homogeneity, and consequently used a random effects model to pool the data.[13,16,28,31] As clinical heterogeneity was present in all of these reviews, and

Table 3.4: AMSTAR Quality assessment of systematic reviews

AMSTAR items	Wilson 2003	Sopo 2004	Olaguibel 2005	Wilson 2005	Penagos 2006	Cox 2007	Hoeks 2007	Calderon 2008	Larenas-Linnemann 2008	Röder 2008
1. Was an 'a priori' design provided?	YES	NO	NO	YES	NO	NO	NO	NO	NO	NO
2. Was there duplicate study selection and data extraction?	NO	YES	YES	NO	YES	NO	YES	NO	NO	YES
3. Was a comprehensive literature search performed?	YES	YES	YES	YES	YES	NO	YES	NO	YES	YES
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	YES	NO	NO	YES	YES	NO	NO	NO	YES	YES
5. Was a list of studies (included and excluded) provided?	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
6. Were the characteristics of the included studies provided?	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES
7. Was the scientific quality of the included studies assessed and documented?	YES	YES	NO	YES	YES	NO	YES	NO	NO	YES
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	NO	YES	NA	NO	YES	NA	YES	NA	NA	YES
9. Were the methods used to combine the findings of studies appropriate?	NO	NA	NO	NO	NO	NA	NA	NA	NA	NA
10. Was the likelihood of publication bias assessed?	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
11. Was the conflict of interest stated?	YES	NO	NO	NO	YES	NO	NO	NO	YES	NO
TOTAL	7	5	3	5	7	1	5	1	3	6
Proportion of applicable items	7/11	5/10	3/10	5/11	7/11	1/9	5/10	1/9	3/9	6/10

NA= not applicable

acknowledged by the authors in two cases [13,28], the reviews received a negative score on this item. The other reviews did not pool results.

None of the reviews reported measures to avoid publication bias. Three of the 10 reviews provided information about the sources of funding, or receiving grants from industry.[13,16,27]

Of the 10 reviews, 6 had an overall score between 5 and 8, indicating a review of moderate quality. Both the Cochrane review (2003) [13] and the review of Penagos et al. [16] scored high, with 7 out of 11 points, followed by Röder et al. with 6 out of 11 points.[29] Four reviews obtained scores of 4 or less, indicating a low quality.[24,25,27,28] The mean AMSTAR score was 4.3 (SD 2.2), indicating that the quality of the systematic reviews is, on the whole, only low to moderate. Adjustment for the number of applicable items (bottom row of Table 3.4) yielded very similar results.

DISCUSSION

The aim of this study was to appraise the quality of systematic reviews and meta-analyses evaluating the efficacy of SLIT in children. Between 2000 and 2008 there was an increase in published systematic reviews, with an overlap of effects and conclusions.

Strengths

Our systematic review on SLIT in children with allergic rhinitis is the first to provide insight into methodological quality of the reviews and meta-analyses measured with a validated checklist. Two reviewers performed quality assessment and data extraction independently.

Limitations

A limitation of the AMSTAR instrument (and many others) is that it does not distinguish between an item that has not been reported, and an item that has not actually been done. Because only information published in the reviews was used, we might have underrated the quality of the reviews. Also, a 'No' for an item may not necessarily be a marker of poor review quality. For example, if no list of excluded studies is reported (Item 5) this may be due to restrictions in the length of the article, rather than to poor reporting.

Although we used an extensive search strategy, our 'review of reviews' could be subject to publication bias. For example, reviews might have been conducted, but not (yet) published. In selecting a specific period (2000-2008) for our search we evidently omitted any reviews published outside this period.

From our initial search, we had to exclude many articles because they did not fulfil our inclusion criteria, a situation not uncommon in literature searches. When designing a search strategy, it is recommended not to be too restrictive in the initial search.[35] Most excluded papers did not provide any details about the search strategy, nor what databases or time period were searched.

A variety of search strategies were used, which were not always clear or adequate. For example, searches using less specific terms will identify other study types or other topics.[37] A systematic review should be transparent and reproducible by providing the complete search strategy. This should include terms describing the target population and the intervention of interest. In addition, authors should use the list of synonyms that can be found in the search database.[38-40]

The importance of evaluating the methodological quality of primary studies has been emphasized before, as it may reduce methodological problems, such as the lack of inadequate randomization methods, and concealment of treatment allocation. [41] In the present study, more than 50% of the authors of the reviews evaluated the methodological quality of the primary studies in an appropriate way, which is needed to assess the risk of bias in the included studies. Four different methods were used. A large variety of methods are used to evaluate the methodological quality of randomized trials.[32,34,35] More consensus is needed to increase comparability.

Although the number of systematic reviews on the efficacy of SLIT in children has increased, many have methodological flaws. For example, some did not include unpublished and foreign-language literature. There is abundant evidence that randomized trials with "positive" results (favouring the new treatment) are published more often and quicker than trials with negative results (finding no difference of favouring the old treatment).[42-47] None of the reviews addressed publication bias, and some did not assess the quality of the studies included in the review. These methodological limitations could have been avoided by using standards such as provided in the Cochrane Handbook for Systematic Reviews of Interventions or Quality of Reporting of Meta-analyses (QUOROM).[35,48]

To assess the quality of the systematic reviews, we considered several methods, such as the Overview Quality Assessment Questionnaire (OQAQ) by Oxman and Guyatt [49] and AMSTAR.[20-22] We chose the AMSTAR instrument, as it builds upon previous tools, empirical evidence and expert consensus and was tested thoroughly by its developers.[20-22]

This study revealed an overall low to moderate methodological quality of systematic reviews, with 40% of the reviews having a score < 4, and no reviews of high methodological quality. The mean AMSTAR score of 4.3 (SD 2.2) indicates that the quality of the systematic reviews is, on the whole, only low to moderate. Moreover, the quality of reviews has not improved in recent years.

Discussion continues regarding the use of individual component scores or summary scores of a checklist.[50,51] The developers of the AMSTAR aimed to develop an instrument that is pragmatic and of value to decision makers. They ensured that the components do not overlap, and validated the total score against an external standard. The component scores measure different domains of quality and the overall score is a summary measure.[20-22]

Not all systematic reviews contain a meta-analysis. Four of the included reviews pooled results.[13,15,28,31] Within the field of sublingual immunotherapy, there is a debate on heterogeneity of meta-analyses on SLIT. In general, the major barrier is that the results of a meta-analysis of heterogeneous studies are difficult to interpret.[52] If significant (statistical or clinical) heterogeneity is present and can be explained, pooling of data should not be considered.[35] As illustrated by Malling, heterogeneity can impair the results of meta-analyses despite accordance with statistical guidelines.[53] Given the clinical heterogeneity of the studies (different allergens, different age groups, different durations) included in the four reviews, pooling the results was considered inappropriate.[35]

Before evaluating the quality of systematic reviews and meta-analyses, we should take a step backwards and look at the fundamental elements of systematic review or meta-analyses, the included studies. Well-conducted randomized clinical trials provide the best evidence on the efficacy of medical interventions. A quality assessment of randomized clinical trials is essential in conducting meaningful systematic reviews.[57] Within the field of immunotherapy, the last couple of years, the essential for proper evaluation of interventions became well-defined. This resulted in guidelines and a checklist for trials with allergen specific immunotherapy. In 2007, Bousquet and colleagues presented a paper which critically described how to conduct clinical trials in immunotherapy.[58] The methodology of randomized clinical trials is essential to assess and register treatment interventions. They concluded very few trials met the criteria for pivotal studies. Also in 2007, Canonica et al made recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy.[59] This paper summarized the recommendations for study design, patients' selection, appropriate outcomes and statistical treatment to be used in planning and performing clinical trials with specific immunotherapy. In the context of conducting and reporting trials in allergen specific immunotherapy, in 2009 Bousquet et al reflected on the items that should be included in the CONSORT checklist [56] for reporting trials in allergen-specific immunotherapy.[60]

Conclusions about the effectiveness of SLIT should be regarded with caution because of the methodological limitations of the reviews and the outcome evaluations on which they are based. From this point of view, in 2009, two meta-analyses reported on SLIT for allergic respiratory diseases [54] and on specific immunotherapy for respiratory allergy.[55] Although both discussed the importance of methodological issues in meta-analyses (e.g. publication bias and heterogeneity), the conclusions of the two meta-analyses differ.

Nieto et al. reported that the current evidence is not strong enough to support routine treatment with SLIT because the meta-analyses supporting it show features suggesting publication bias and show inconsistent and discrepant conclusions.[54] However, Compalati et al. stated that, according to evidence-based criteria, specific immunotherapy can be recommended for the treatment of respiratory allergy because of its efficacy in reducing asthma and rhinitis symptoms.[55]

Since our search in 2008, several large randomised trials in children have been published that contribute to the overall balance of evidence for SLIT in children, mainly for grass allergens.[61-65] Although we did not formally evaluate these trials, the overall reporting quality seems to be improving. A future update of this review should answer this question in a more systematic way.

CONCLUSIONS

To evaluate the efficacy of SLIT in children a systematic review is useful. Although the number of systematic reviews on SLIT has increased, the methodological quality remains limited and could be improved. SLIT for children could be promising, but methodological flaws in the reviews and the individual studies are too serious to draw balanced conclusions. In order to ensure complete and transparent reporting of randomized controlled trials, future studies must comply with guidelines as described. This provides more valid estimates of treatment effects and may serve as a reliable basis for the development of evidence-based guidelines.

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Chapter 4

Randomized double-blind placebo-controlled trial of sublingual immunotherapy in children with house dust mite allergy in primary care: study design and recruitment

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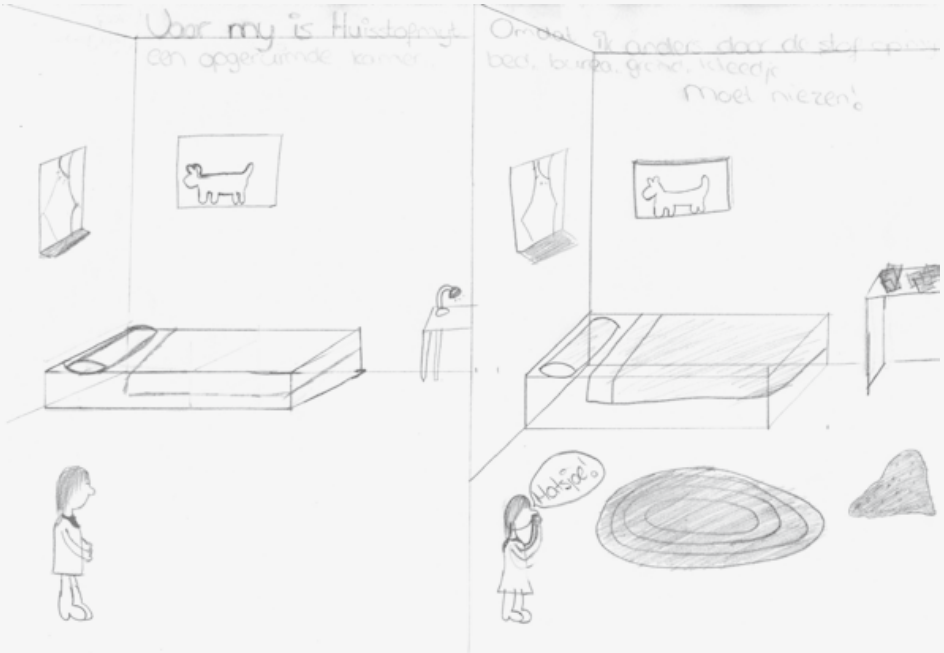

ABSTRACT

Background

For respiratory allergic disorders in children, sublingual immunotherapy (SLIT) has been developed as an alternative to subcutaneous immunotherapy (SCIT). SLIT is more convenient, has a good safety profile and might be an attractive option for use in primary care. A randomized double-blind placebo-controlled study was designed to establish the efficacy of SLIT with house dust mite allergen compared to placebo treatment in 6 to 18-year-old children with allergic rhinitis and a proven house dust mite allergy in primary care. Described here are the methodology, recruitment phases, and main characteristics of the recruited children.

Methods

Recruitment took place in September to December of 2005 and 2006. General practitioners (in south-west Netherlands) selected children who had ever been diagnosed with allergic rhinitis. Children and parents could respond to a postal invitation. Children who responded positively were screened by telephone using a nasal symptom score. After this screening, an inclusion visit took place during which a blood sample was taken for the RAST test. Trial registration: the trial is registered as ISRCTN91141483 (Dutch Trial Register).

Results

A total of 226 general practitioners invited almost 6000 children: of these, 51% was male and 40% <12 years of age. The target sample size was 256 children; 251 patients were finally included. The most frequent reasons given for not participating were: absence or mildness of symptoms, absence of house dust mite allergy, and being allergic to grass pollen or tree pollen only. Asthma symptoms were reported by 37% of the children. Of the enrolled children, 71% was sensitized to both house dust mite and grass pollen. Roughly similar proportions of children were diagnosed as being sensitized to one, two, three or four common inhalant allergens.

Conclusion

Our study was designed in accordance with recent recommendations for research on establishing the efficacy of SLIT; 98% of the target sample size was achieved. This study is expected to provide useful information on SLIT with house dust mite allergen in primary care. The results on efficacy and safety are expected to be available by 2010.

BACKGROUND

Specific immunotherapy with allergens might prevent the onset of asthma in individuals with allergic rhinitis and may accelerate the remission of asthma in children with allergic disease.[1-3] Although subcutaneous immunotherapy (SCIT) is an effective treatment of respiratory allergic disorders[4], the injections can be uncomfortable and side effects, though rare, may be serious and even fatal.[5,6] The use of specific sublingual immunotherapy (SLIT) for treatment of respiratory allergic disorders in children may be a viable alternative to SCIT because of its convenient form of administration and good safety profile - which has allowed home administration of SLIT.[7,8] Thus, although SLIT seems particularly suitable for children in primary care, most clinical trials up to now have been performed in a hospital setting.

Evidence for the efficacy of SLIT in children remains inconclusive. Various reviews concluded that there was insufficient evidence to recommend SLIT for use in routine clinical practice.[9-11] In their Cochrane review, Wilson et al. concluded that SLIT is an accepted treatment for adults; studies with children revealed no significant reduction in symptoms and medication scores, but the number of participants was small.[12]

In 2001, the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines were published in co-operation with the World Health Organization.[13] They recommend treatment of allergic rhinitis in a stepwise manner (using a combination of allergen avoidance, pharmacotherapy and immunotherapy) based on the duration and severity of disease, rather than on the type of exposure (i.e. seasonal, perennial, occupational) as in previous guidelines.[14] Immunotherapy is recommended for patients with more severe disease, for those not responding to usual treatments, or for those refusing usual treatments; this type of patient is generally treated in a hospital setting and/or by a specialist.

In the Netherlands, allergic rhinitis in children is usually managed by the general practitioner (GP). We hypothesized that SLIT could be an effective treatment in primary care and designed a study to evaluate the efficacy and safety of SLIT in children and adolescents with house dust mite-induced allergic rhinitis. Here we describe the methodology, recruitment, and main characteristics of the primary care study population.

METHODS

Study design

This ongoing study is a randomized double-blind placebo-controlled study, comparing the efficacy of SLIT with house dust mite allergen (SLIT-HDM) to that of placebo treatment in 6 to 18-year-old children with allergic rhinitis and a proven house dust mite allergy in primary care. Patients entered the study and started treatment either in

September-December 2005 or in September-December 2006 for a period of approximately two years. Written informed consent was obtained. The study was approved by the Ethical Review Board of Erasmus MC-University Medical Center Rotterdam. The trial was registered as ISRCTN91141483.

Participants and recruitment

GPs in south-western Netherlands selected children aged 6 to 18 years in their computerized patient files with either a diagnosis of hay fever/allergic rhinitis or relevant medication use: i.e. antihistamines for systemic use; nasal corticosteroids; topical decongestants; topical anti-allergics, and other nasal preparations.

Recruitment took place September to December in 2005 and in 2006. An information letter signed by the GP was sent to the selected children. This letter described the general purpose of the study, elicited cooperation, and provided a return form and envelope. On the return form children and parents could indicate whether or not they were interested in the study; if not interested they could indicate the reason for not participating.

Participants who responded positively were telephoned by a research assistant to arrange a screening interview (see below). The research assistant asked questions about nasal symptoms during the last three months, the history of allergic rhinitis, general medication use, and use of asthma medication. Table 4.1 gives an overview of all inclusion and exclusion criteria.

After telephone screening an inclusion visit took place for those who met the inclusion/exclusion criteria and who agreed (children/parents) to further participation. During this visit, the research assistant performed/recorded the following: rhinitis symptoms during the last month and last week (nasal symptoms: rhinorrhea, blocked nose, sneezing, itching); conjunctivitis symptoms during the last month and last week (eye symptoms: tearing, itching, redness); International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [15] for rhinitis and asthma; wheeze and cough; family history of allergy, asthma and eczema; rhinoconjunctivitis-specific quality of life for pediatrics and adolescents (PRQLQ and AdolRQLQ)[16,17]; blood sample for RAST (grass pollen, tree pollen, HDM, cat dander and a pet, if present at home) (CAP-Phadiatop®, Pharmacia Diagnostics AB, Uppsala, Sweden); and physical examination (weight and height).

After the screening visit, when children met the inclusion criteria and none of the exclusion criteria and children and parents agreed to participate, a home visit was scheduled to provide instructions about the baseline diary. Every day for one month, children recorded the symptoms related to allergic rhinitis on a diary card; also reported were other complaints, rescue medication, and other medication needed (see below). At this visit the research assistant took dust samples from the child's bedroom floor and mattress to assess indoor HDM exposure. This will be repeated after two years.

Table 4.1: Inclusion and exclusion criteria for the study population

Inclusion criteria
• aged 6-18 years
• history of allergic rhinitis for at least 1 year
• IgE antibodies ≥0.7 kU/l to house dust mite
• no use of nasal steroids in the month before start of baseline measurements
• rhinitis symptom score of at least 4 out of 12 during last 3 months
• signed informed consent
Exclusion criteria
• severe asthma (requiring 800 mcg budesonide daily or equivalent for other inhaled steroids; or requiring >3 courses of oral prednisone/prednisolone in previous year or required hospital stay for asthma in previous year)
• sensitization to pets present at home (IgE antibodies ≥0.7 kU/l)
• planned surgery of nasal cavity
• having received immunotherapy in past 3 years
• language barrier
• contraindications to sublingual immunotherapy (as supplied by the manufacturer)

After the baseline diaries had been completed a new visit was scheduled and, after signing informed consent, participants were assigned to SLIT treatment or placebo according to the randomization schedule (see below).

Randomization

Randomization was generated by a computer program in varying block sizes unknown to the investigators. The randomization list was passed to the Department of Pharmacy at Erasmus MC. In order to ensure that disease severity was similar between patients assigned to verum therapy and those assigned to placebo, randomization was stratified according to severity on the basis of data obtained during the telephone screening.

Intervention

Participants received an aqueous extract of house dust mites (*Dermatophagoides pteronyssinus*) in a glycerinated isotonic phosphate buffered solution (Oralgen Mijten, Artu Biologicals, Lelystad, the Netherlands) or placebo treatment consisting of the glycerol solvent. In accordance with the manufacturer's guidelines the treatment period was divided into two phases: a dose escalation phase of 20 days, and a maintenance phase of approximately two years. Treatment started on day one with a single drop. One drop consisting of 0.05 ml corresponds with 35 biological units (BU); the dose was increased by one drop per day until day 20 (20 drops = 1 ml = 700 BU). The maintenance dose was 20 drops (=700 BU) twice weekly. The drops were administered sublingually and kept there for at least 1 minute before being swallowed. A research assistant instructed the

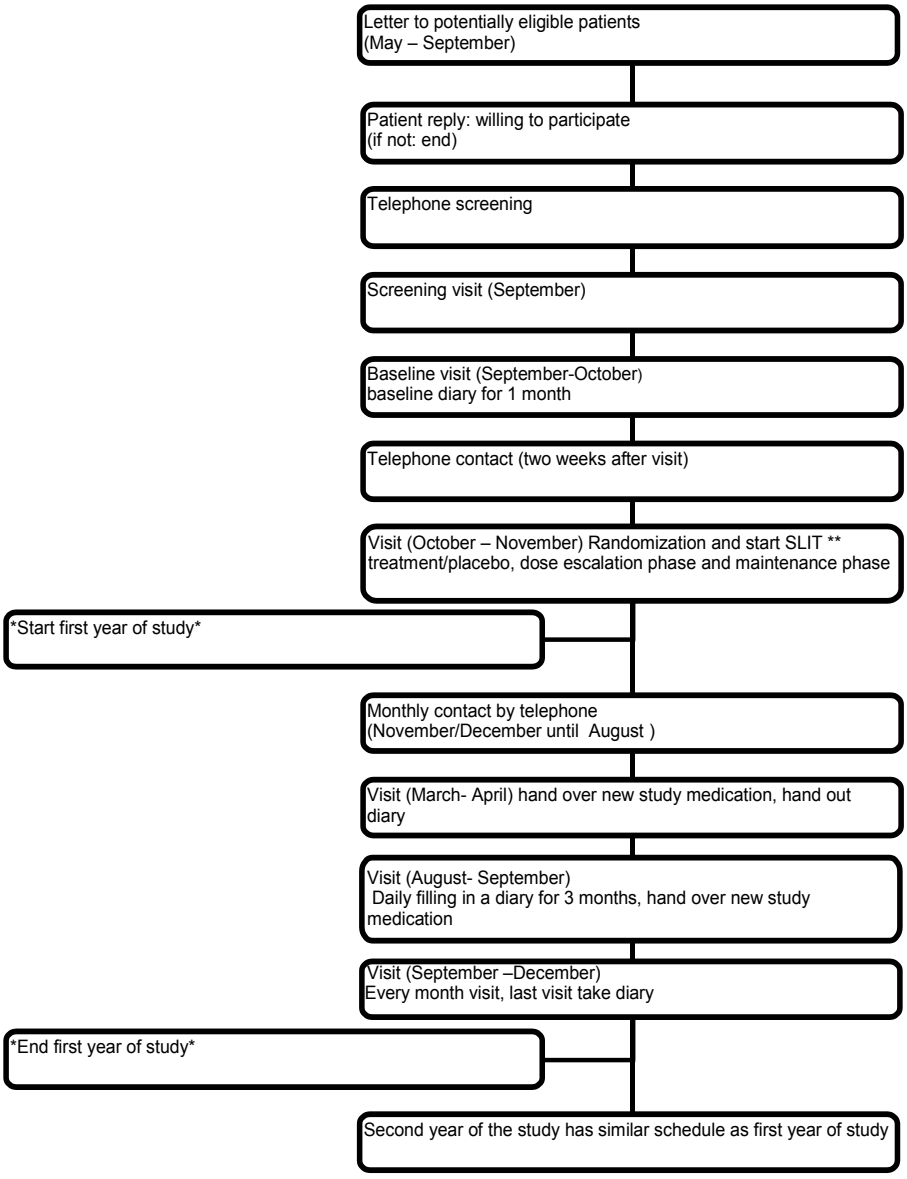

Figure 4.1: Detailed time schedule per individual patient
** informed consent: 6-11 years child assents and parents' consent, 12-17 years child assents/consents and parents' consent

participants and also provided written instructions. Participants, parents, investigators, research assistants and caregivers were blinded to treatment allocation.

Follow-up

Figure 4.1 shows the time schedule per individual patient. After randomization children started with treatment for 20 days (dose escalation phase) followed by a maintenance phase of two years. Children filled in a diary during three months (between September and December) after one and two years of treatment (see below). Every month a research assistant completed a questionnaire (conducted by telephone) throughout the entire

study period. Over the two years of treatment the total number of planned contacts is 13 home visits and 23 telephone calls.

Outcome measures

The primary outcome measure for efficacy is the difference between the group receiving SLIT and the group receiving placebo for the total daily mean rhinitis symptom score for four nasal symptoms (see below), assessed through a diary filled in during three months after two years of treatment. In the period of evaluation (September through December), the percentage of days on which the daily symptoms are properly recorded should be at least 50%. For patients who do not meet this criterion in the second year (e.g. dropouts after 1 year) data of the first treatment year will be used. See section Data analysis for further details.Secondary outcome measures are the difference between the group receiving SLIT and the placebo group for the proportion of symptom-free days, the proportion of rescue medication-free days, use of rescue medication, mean eye symptom score, total symptom score (nasal and eye symptoms), and disease-specific quality of life after two years of treatment. Overall evaluation of the treatment effect will be assessed by patient, parents and research assistant after two years of treatment.

Assessment of efficacy

Efficacy will be measured by patient-assessed symptom scores. Although nasal, eye, skin and lung-related symptoms have been related to house dust mite allergy, the main allergic symptoms are considered to be the following nasal symptoms: sneezing, itching, watery running nose and blockage. The intensity of these symptoms is subjectively assessed according to a grading scale: 0 = no complaints, 1 = minor complaints, 2 = moderate complaints and 3 = serious complaints; the maximum score is 12. The scores will be assessed daily by the patient and recorded in the patient's diary. The period of measurement will be three months in the period September through December in 2006 and 2007 for the primary outcome measures (first cohort), and in 2007 and 2008 (second cohort); this autumnal period of the year was chosen because it has the highest HDM exposure levels.

Assessment of safety, tolerability and compliance

Adverse effects will be assessed by patients and parents reporting effects in the diary, or calling the research assistant with complaints, or by the research assistant via a questionnaire filled in during home visits, and by monthly telephone contact. All adverse events reported during the study will be recorded. In case of serious adverse events or persisting allergic symptoms after management according to protocol, the study treatment will be discontinued for these patients. If patients discontinue the study medication,

they will be asked to agree to further follow-up according to the study protocol during the remainder of the study period.

Compliance will be measured by self-report of SLIT administration in the diary and by monthly telephone contact, and determined by weighing the returned study medication.

Sample size calculation

As rhinitis symptoms are the primary outcome measure, this was used for calculating the sample size. A Dutch study on mattress covers provides relevant data for symptom scores in patients with house dust mite allergy (aged 8-50 years).[18] Based on the baseline symptom score in the latter study, and the ability to assess a reduction of at least 30% (proposed by Malling as a clinically relevant reduction)[19], in our study a sample size of 96 patients per group would be required. Taking into account a dropout rate of 25% between randomisation and end of follow-up, this would require 128 patients in each study group. An alternative approach is assuming the nasal score at the last week screening visit to be 4.5 (sd 2.6). A 30% change would provide a delta of approximately 0.5 (generally assumed to be clinically relevant) and require a sample size of 105 per study group (alpha = 0.05 and beta = 95%).

Quality of life

Rhinoconjunctivitis-specific quality of life will be assessed through the validated Pediatric (6-11 years) and Adolescent (12-17 years) Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ and AdolRQLQ, respectively) at baseline and after one and two years.[16,17] To establish the presence of lower airway symptoms during the last 12 months at baseline, specific questions on wheezing and dry cough at night were taken from the ISAAC.[15]

Rescue medication

During the study the use of symptomatic allergy medication is discouraged, especially use of long-acting antihistamines and locally or generally administered corticosteroids. However, rescue treatment is allowed in case of persisting allergic symptoms (levocetirizine tablets, xylomethazoline nasal spray and levocabastine eye drops); the above-mentioned rescue medication will be provided free of charge. In principle, patients are encouraged to use the provided medication only, but are allowed to use their own medication as well. Patients were clearly instructed on the use of rescue medication and other medication, and on how to document entries in the patient diary. For severe or steadily worsening rhinoconjunctivitis symptoms or intermittent asthma the patient should consult his/her physician.

Data analysis

The treatment effect will be tested at a two-sided significance level of 5%. Statistical comparison between verum and placebo of the mean daily sum score from the diary after two years will be done using Analysis of Covariance. There will be three covariates in this analysis: baseline nasal sum score at entry into study, age of patients, and presence of cat allergy. In case more than one child from the same family has been included in the study and contribute to the final analysis, we will test whether 'family' provides a statistically significant effect ($P<0.20$). In that case 'family' will be added as a random effect.

Exploratory subgroup analyses are planned for the difference between placebo and verum regarding the primary outcome according to age and the baseline symptom score (both dichotomized at the median value).

All analyses will be performed according to the intention-to-treat principle, i.e. irrespective of compliance with the prescribed dosing schedule and other treatments, but excluding patients in whom major inclusion criteria were not fulfilled. A per-protocol analysis will include all patients who took at least 80% of the study medication and completed 50% of the diaries.

For this paper, the distribution of age and gender throughout the recruitment period will be compared. All data are presented as summary descriptive statistics: means, standard deviations (SD) or percentages. Statistical analyses were carried out with SPSS version 11.0 and differences of $p<0.05$ were considered significant.

RESULTS

Letters were posted by 226 general practitioners to 5986 children. An answer form was returned by 2555 children; of these, 1072 children responded positively to the letter and 500 of these children were included after the screening by telephone. Finally, 251 children (i.e. only 4.2% of the children selected in general practice) were included in the study.

Table 4.2 summarizes the main reasons given for not participating in the consecutive recruitment phases. In response to the initial mailing most of those who declined had few or no complaints (48%), or had another allergy (16%). During the telephone screening, those not included had no history of HDM allergy (28%) or a low symptom score (28%). In the last phase of the recruitment (the screening visit) the main reasons for non-participation were no HDM allergy but only grass or tree pollen allergy detected by RAST (33%), and no sensitization to inhalant allergens detectable by RAST (30%).

Table 4.3 presents the baseline characteristics of the included patients. The mean age of the participants was 11.8 (SD 3.0) years. A total of 251 children were randomized

Table 4.2: Reasons not to participate in the consecutive recruitment phases

Reasons not to participate	Total (n)	Percentage
Letter returned (n=1483)		
Few or no complaints	710	48.4%
Other allergy	240	16.4%
Study too burdensome	202	13.8%
No interest in the study	186	12.6%
No reason	145	9.8 %
Telephone screening (n=572)		
No HDM allergy	159	27.8%
Low symptom score (<4/12)	158	27.6%
Not interested in study	57	10.0%
Severe asthma	39	6.8%
Language barrier	27	4.7%
Use of immunotherapy in the last 3 years	19	3.3%
Refusing blood sample to be taken	17	3.0%
Age (out of range)	15	2.6%
Allergic complaints <1 year	12	2.1%
History of severe allergic reaction	9	1.6%
Systemic disease	8	1.4%
Use of nasal corticosteroids 1 month before baseline	7	1.2%
Answer forms received after deadline of inclusion period	45	7.9%
Screening visit (n=249)		
Only grass pollen or tree pollen sensitization	81	32.5%
No sensitization detectable	75	30.1%
Sensitive to pet at home (confirmed by RAST)	60	24.1%
No informed consent	29	11.7%
Use of unallowed co-medication	4	1.6%

to treatment or placebo. During the recruitment period nasal complaints were assessed at several time points; this symptom score showed a difference between telephone screening (6.8) and screening visit (4.5). More than half of the children reported wheeze/breathlessness (54%) and dry cough (53%) during the last year. In almost 37% of the children asthma was reported.

The majority of the children (77%) were multisensitized. Roughly similar proportions of children were diagnosed as being sensitized to one, two, three or four common allergens. Of the included children, 71% was sensitized to both HDM and grass pollen, followed by tree pollen in 43%, and cat dander in 34% of the children.

Table 4.4 shows the distribution of age and gender during the recruitment process.

Table 4.3: Baseline characteristics of the included children

	Total (n=251)	Percentage
Gender		
Male	149	59.4%
Female	102	40.6%
Age Mean (SD) in years: 11.8 (3.0)		
6-11 years	122	48.6%
12-17 years	129	51.4%
Physical characteristics		
Weight in kg: mean (SD)	47.5 (15.3)	
Height in cm: mean (SD)	154.6 (17.1)	
Season with most complaints of allergy		
Spring	35	13.9%
Autumn	14	5.6%
Spring and autumn/entire year	201	80.1%
Nasal symptoms (scale 0-12)		
Telephone screening: mean (SD)	6.8 (2.1)	
Screening visit in last 3 months: mean (SD)	5.8 (2.3)	
Screening visit in last week: mean (SD)	4.5 (2.6)	
Asthma		
Asthma present	92	36.7%
Asthma medication	99	39.4%
Wheeze/breathless - ever	154	62.3%
Wheeze/breathless - last year	131	53.9%
Dry cough at night - last year	130	52.6%
Sensitization		
One allergen (monosensitized for HDM)	58	23.1%
Two allergens	67	26.7%
Three allergens	72	28.7%
Four allergens	54	21.5%
Sensitization to both HDM and		
Grass pollen	179	71.3%
Tree pollen	108	43.0%
Cat dander	85	33.9%

Of almost 6,000 children, 51% was male and 40% was aged 6-11 years. In the final recruitment phase, 251 children were included in the study. The distribution of age (6-11 years, $p=0.006$) and gender (boys 59%, $p<0.025$) of the children included in the present study is significantly different from those who initially received the invitation letter.

Table 4.4: Distribution of age and gender during the recruitment phases

	Total	Male		Age group 6-11 years	
	n	n	%	n	%
Total mailed	5986	3066	51.2%	2369	39.6%
Letter returned (irrespective of answer)	2555	1331	52.1%	1036	40.5%
Letter returned positive response	1072	592	55.2%	471	43.9%
Telephone screening positive	500	279	55.8%	214	42.8%
Screening visit positive	251	149	59.4% [1]	122	48.6%2

1: p = 0.006 (compared with 5986 children who were initially contacted)
2: p = 0.025 (compared with 5986 children who were initially contacted)

DISCUSSION

This is an ongoing randomized double-blind placebo-controlled trial to establish the efficacy of sublingual immunotherapy with house dust mite allergen in children in primary care. Because the effectiveness of SLIT is still under discussion (mainly due to inconclusive quality/methodology of the published trials), the present long-term study is expected to provide useful information about SLIT with house dust mite allergen in primary care.

Although the distribution of age and gender of the participating children is significantly different from those contacted in the first recruitment phase, the difference is relatively small and age and gender groups are adequately represented; therefore, this difference should not affect the generalizability of the results of the trial.

Strengths and weaknesses

The importance of the methodology and quality of immunotherapy trials has been documented.[19] The present study has a baseline assessment and complies with other recommendations: i.e. placebo-controlled, double-blind, randomized, adequate sample, sufficient duration of treatment, patients selected according to predefined clinical criteria, and clearly defined primary and secondary outcomes.

Most related studies have been performed in a hospital setting [20,21], so that the results may not be applicable to the general population. Therefore, our study is designed to evaluate - in a primary care setting - the efficacy and safety of SLIT in children and adolescents with house dust mite-induced allergic rhinitis.

The ARIA guidelines propose that SLIT can be administered to young patients if these children are carefully selected with rhinitis, conjunctivitis and/or asthma caused

by pollen and mite allergy.[13] By recruiting young children from a primary care setting (according to our methodology) the included children will meet this recommendation.

Most earlier studies failed to report on the phase prior to randomization, whereas the present study reports the reasons given not to participate and possible selection bias.

According to the WAO Task Force, the ideal efficacy study of specific allergen immunotherapy should be performed in monosensitized patients or in patients concomitantly sensitized to noncross-reacting allergens.[22] It is reported that single-allergen-specific immunotherapy may prevent sensitization to other airborne allergens in monosensitized children.[1,3,23] In our study we included both monosensitized and multisentized children; the majority was multisensitized and only 23% was monosensitized. We believe that this will increase the generalizability of the study results to a wider range of patients.

Many clinical trials face recruitment problems and have to approach many patients in order to include only a small proportion.[24,25] In a survey of 78 studies in Dutch primary care, a median of 87% of planned patients was recruited.[26] In the present study 98% of the target sample size was recruited.

Conclusion

Our study was designed in accordance with recent recommendations for research on establishing the efficacy of sublingual immunotherapy; 98% of the target sample size was reached. This study is expected to provide useful information on the position of SLIT with house dust mite allergen in primary care.

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Chapter 5

Sublingual immunotherapy not effective in house dust mite allergic children in primary care

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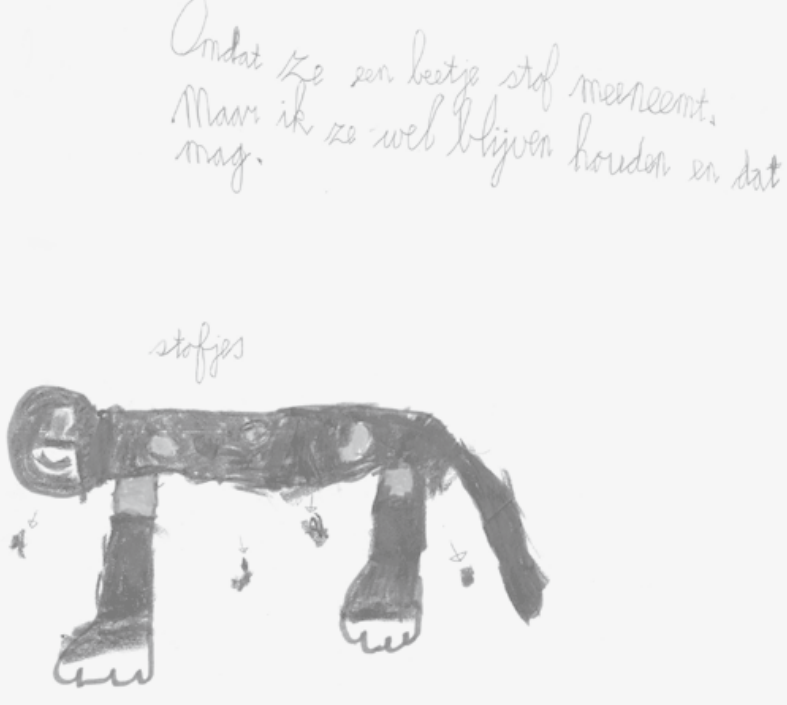

ABSTRACT

Background

Sublingual immunotherapy (SLIT) as a therapy for treatment of allergic rhinitis in children might be acceptable as an alternative for subcutaneous immunotherapy. However, the efficacy of SLIT with house dust mite extract is not well established.

Objective

To investigate whether SLIT in house dust mite-allergic children recruited in primary care is effective and safe.

Methods

Children aged 6-18 years (n=251) recruited in primary care with a house dust mite-induced allergic rhinitis received either SLIT or placebo for 2 years. Symptoms and medication use were assessed throughout the study. Primary outcome parameter was the mean total nose symptom score (scale 0-12) during the autumn of the second treatment year. Safety was assessed by recording any adverse event.

Results

Overall, the mean nose symptom score ± SD after 2 years of treatment showed no significant effect of SLIT (symptom score intervention group 2.26 ± 1.84 vs. placebo group, 2.02 ± 1.67; p=0.08). There were no significant differences in secondary outcomes, nor in subgroup analyses. The number of patients reporting adverse events was comparable between both groups.

Conclusion

SLIT with house dust mite allergen was not better than placebo in reducing rhinitis symptoms in house dust mite-allergic children in primary care. SLIT as administered in this study can be considered safe.

INTRODUCTION

Allergic rhinitis is a common disorder in children. House dust mite (*Der. p1 and Der. f1*) is the most frequent indoor allergen causing this condition.[1,2] Unlike grass and tree pollen, house dust mites are present all year around with a peak in autumn.[1,2] National and international guidelines have recently been developed to improve the management of patients with allergic rhinitis.[3-6]

Allergen immunotherapy is available in different modes of administration.[7] Subcutaneous immunotherapy (SCIT) has been the most applied route for several decades and is effective in adults, but carries a risk of severe side effects.[8,9] For children, there are important advantages of using sublingual immunotherapy (SLIT) as a treatment. SLIT has a convenient form of administration and a good safety profile which allows home administration.[10-13]

Specific immunotherapy might prevent the onset of asthma and new sensitizations, and may accelerate the remission of asthma in children with allergic disease [14-18] Immunotherapy is recommended in the ARIA guidelines for patients with more severe disease, for those not responding to usual treatments, and for those refusing usual treatment.[5,6]

Clinical trials determining the efficacy of SLIT involving children have almost exclusively been performed in referral centers.[19-22] SLIT may also be an effective treatment in primary care, as allergic rhinitis is mostly diagnosed and treated in primary health care. Only one study with SLIT in children recruited in a primary care setting has been performed, and this concerned grass pollen-related rhinoconjunctivitis.[23]

Evidence for the efficacy of SLIT in children with house dust mite-induced allergy remains inconclusive.[24-26] A recent meta-analysis of SLIT house dust mites for respiratory allergy in both adults and children concluded that there is promising evidence of efficacy for SLIT, using mite extract in allergic patients (adults and pediatric population analyzed together). However, analyses in the pediatric population were based on a very small population and conclusions should therefore be interpreted with caution.[27]Our aim was to evaluate the efficacy and safety of two years of treatment with SLIT with house dust mite allergen, compared to placebo treatment, in 6 to 18-year-olds in primary care with house dust mite-induced allergic rhinitis.

METHODS

Study design

The study was a randomized double-blind placebo-controlled trial, investigating the efficacy of 2 years of sublingual immunotherapy with SLIT with house dust mite allergen (SLIT-HDM) compared to placebo in 6 to 18-year-old children with allergic rhinitis and

a proven house dust mite allergy in primary care. Patients entered the study during September-December in 2005 or in 2006. Written informed consent was obtained from parents of all children and from children aged 12-18 years. The study was approved by the Ethical Review Board of Erasmus MC. A detailed description of the design of the study has been published elsewhere and is summarized below.[28] The trial was registered as ISRCTN91141483 (Dutch Trial Register).

Patients

Children aged 6-18 years with at least a 1-year history of allergic rhinitis were invited by their general practitioner (GP) for this study. Children were screened by researchers of Erasmus Medical Centre according to the following predefined criteria. Children were enrolled only if they had IgE antibodies ≥0.7 kU/l to house dust mite (CAP-Phadiatop®, Pharmacia Diagnostics AB, Uppsala, Sweden. HDM CAP class 2: 0.7-3.5 KU/l; class 3: 3.5-17.5 KU/l; class 4: 17.5-50 KU/l; class 5: 50-100 KU/l; class 6: > 100 KU/l); did not use nasal steroids in the month before start of baseline measurements; had a retrospective nose symptom score of at least 4 out of 12 points during the last 3 months; and provided written informed consent.

Patients were excluded when they had been treated with immunotherapy in the previous 3 years; had severe asthma (defined as requiring 800 mcg of budesonide or equivalent other inhaled corticosteroid daily; or had required >3 courses of oral prednisone/prednisolone, or one or more hospital admissions for asthma in the previous year; had a sensitization to pets present at home at entry in the study (IgE antibodies ≥0.7 kU/l), or had a planned surgery of the nasal cavity.

SLIT

In the currently marketed Oralgen® House Dust Mite (Artu Biologicals, Lelystad, the Netherlands), the content of active substance is declared as Biological Units (BU), based on in vivo standardization compared to the D. pter house dust mite in house reference extract of the manufacturer. To assess the concentration of Der. p1 and Der. f1 (mcg/ml) in the study medication, three vials of the active study drug and placebo medication were analyzed. Concentration of Der. p1 and Der. f1 was determined by making use of the Der. p1 and Der. f1. ELISA kit (Indoor Biotechnologies, Warminster, UK) according to the supplier's instructions. Participants received an aqueous extract of house dust mites (D. pter, *Dermatophagoides pteronyssinus*) in a glycerinated isotonic phosphate buffered solution (Oralgen Mijten®) or placebo treatment consisting of the glycerol-containing solvent only. Treatment started on day 1 with 0.05 ml (1 drop) corresponding with 35 BU; the dose was increased by 1 drop per day until day 20 (20 drops = 1 ml = 700 BU). After this dose escalation phase the maintenance dose was 20 drops twice weekly. The drops were administered sublingually and kept there for at least 1 minute before being

swallowed. These instructions were given and monitored during home visits by research assistants of Erasmus Medical Centre.

Outcome measures

The primary outcome measure for efficacy was the difference in total daily mean nose symptom score based on 4 nose symptoms (rhinorrhea, blocked nose, sneezing, itching) between the groups receiving house dust mite allergen extract and placebo, after 2 years of treatment in the period September through December. The intensity of these symptoms was subjectively assessed according to a grading scale: 0 = no complaints, 1 = minor complaints, 2 = moderate complaints and 3 = serious complaints; the maximum score was 12. The scores were assessed daily by the patient and recorded in a diary. The period of assessment of all outcome measurements was a baseline period of 1 month before randomization and 3 months in the period September through December after 1 and 2 years of treatment.

Secondary outcome measures were the differences in the following measures after 2 years of treatment of the active study drug and placebo:

- the proportion of "well days"
- the proportion of symptom-free days
- the proportion of days with rescue medication (medication combined)
- the proportion of days with levocetirizine tablets
- the proportion of days with xylomethazoline nasal spray
- the proportion of days with levocabastine eye drops
- total mean symptom score for nose and eye (symptoms combined)
- total mean eye symptom score
- rhinoconjunctivitis-specific quality of life
- patients' rating of benefit of treatment after two years.

A "well" day was defined in two different ways: 1) as a day without nose symptoms and without rescue medication, and 2) as a day with minimal nose symptoms (maximum 2 points and per symptom not more than 1 point) and without rescue medication.

A symptom-free day was defined in two different ways: as a day with a total nose symptom score of 0, or a day with a combined nose and eye total symptom score of 0.

Rescue treatment (levocetirizine tablets, xylomethazoline nasal spray and levocabastine eye drops) and other medication were documented in a patient diary throughout the two-year period.

For the eye symptom score, the following symptoms were scored: tearing, itching, redness. The intensity of these symptoms was assessed according to the same grading scale as for nose symptoms.

Rhinoconjunctivitis-specific quality of life (QoL) was assessed through the validated Pediatric (6-11 years) and Adolescent (12-17 years) Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ and AdolRQLQ, respectively). The score ranged from 0 (i.e. not troubled) to 6 (i.e. extremely troubled), with lower scores indicating a better QoL.[29,30]

Patients were asked for their overall evaluation of the treatment effect after two years based on the following scale: 1 = much worse, many more complaints, 2 = worse, more complaints, 3 = no difference, similar complaints, 4 = a bit better, less complaints, 5 = much better, hardly any complaints, 6 = no complaints any more.

Safety was assessed by recording any adverse event.

In addition, exploratory analyses were performed for separate nose and eye symptoms (see above), and asthma symptoms after 2 years of treatment. Asthma symptoms were wheezing/dyspnea and dry cough during the night. The intensity of these symptoms was assessed according to the same grading scale as described above.

Compliance

Compliance was determined by weighing the returned study medication. Compliance was calculated over the complete study period.

Populations for analysis

The primary analysis was conducted on the intention-to-treat (ITT) population which included all patients who took at least one dose of study medication and who had evaluable diary data after either 1 or 2 years of treatment (i.e. symptom scores for relevant outcome measure filled out for at least 50% per diary period). The per-protocol (PP) population included all patients who completed the study according to the protocol and had no major protocol violations.

The major protocol violations were:

- Compliance to medication <80%, i.e. using less than 80% of prescribed study medication over the total study period.
- Withdrawal from study/loss to follow-up. In case major events occurred during the study period, which necessitated withdrawal from the study, or loss to follow-up/drop-out for other reasons, diary card data were evaluated up to the day of drop-out. Patients were requested to agree with further follow-up according to the study protocol.
- Diary of second year filled out <50% of days. In the period of evaluation (diary period after 2 years), the percentage of days at which the daily symptoms were properly recorded should be at least 50%.

The safety population included all patients who received at least one dose of the investigational product.

Statistical analysis

A detailed description of the sample size calculation of the study has been published elsewhere.[28] We aimed at a sample size of 128 patients in each study group, allowing for 25% loss to follow-up.Statistical comparison between the active study drug and placebo of the mean daily nose sumscore after 2 years was done using repeated measurements ANOVA (SPPS version 15). Five covariates were included in this analysis: baseline symptom score at entry into study; age of patients at entry into study; gender; house dust mite CAP-class at entry into study (class 2-6); cohort (patients started in 2005 or 2006). In addition, the year of evaluation after start of treatment (first year, second year) was included in the model (YEAR). Baseline symptom score and age were entered as continuous covariates (both retaining 1 decimal), gender as dichotomous (male/female), HDM CAP-class as dichotomous (Class 2 = 0, Class 3-6 = 1) and cohort as dichotomous (Cohort 1, Cohort 2). YEAR represents a fixed factor (first year of evaluation = 1, second year of evaluation = 2). In this model the nose sum score at baseline and after 1 and 2 years was analyzed as square root transformed variables in order to get approximate normal distributions.

The variance-covariance matrix of measurements at two years of follow-up was unstructured. The adjusted means, pairwise treatment differences, p-values and 95% confidence limits for the treatment differences are summarised for the second evaluation year. Repeated measures analysis does not explicitly use any form of imputation. However, all evaluable data (baseline diary, first year of evaluation and second year of evaluation) for a subject were used in the analysis and this method of analysis is generally considered optimal in case the total symptom score is missing either at the first or second year of follow-up.

The distributions of residuals of the main model were checked at the two evaluation years. If the residuals did not appear to follow a normal distribution at one or both evaluation years, as shown by the Shapiro Wilks test with $p<0.01$, bootstrapping was used instead. In this case the primary analysis was done by analysing the symptom scores at the second year, with the observation after 1 year carried forward in case the second year symptom score was missing. The same model was used as described above excluding the terms containing the YEAR variable. Bootstrapping was performed with 5000 replicates using STATA software, version 10 to estimate standard errors, p-values and 95% confidence intervals for the adjusted treatment effect.

Subgroup analysis

We compared the effect of placebo and the active study drug within planned subgroups of patients with a baseline mean total nose symptom score of < 3 and ≥ 3; patients with a RAST class of 2 and above 2; and monosensitized and polysensitized patients. No subgroup analyses were performed to explore whether certain patients benefit more from treatment than others.

RESULTS

Demographic and baseline characteristics

A total of 500 children were screened and 257 patients were randomly assigned to receive either SLIT or placebo therapy. Of the 257 randomized patients, 251 comprised the safety population, 226 the ITT population and 185 patients the PP population. Figure 5.1 shows the flow of patients during the study.

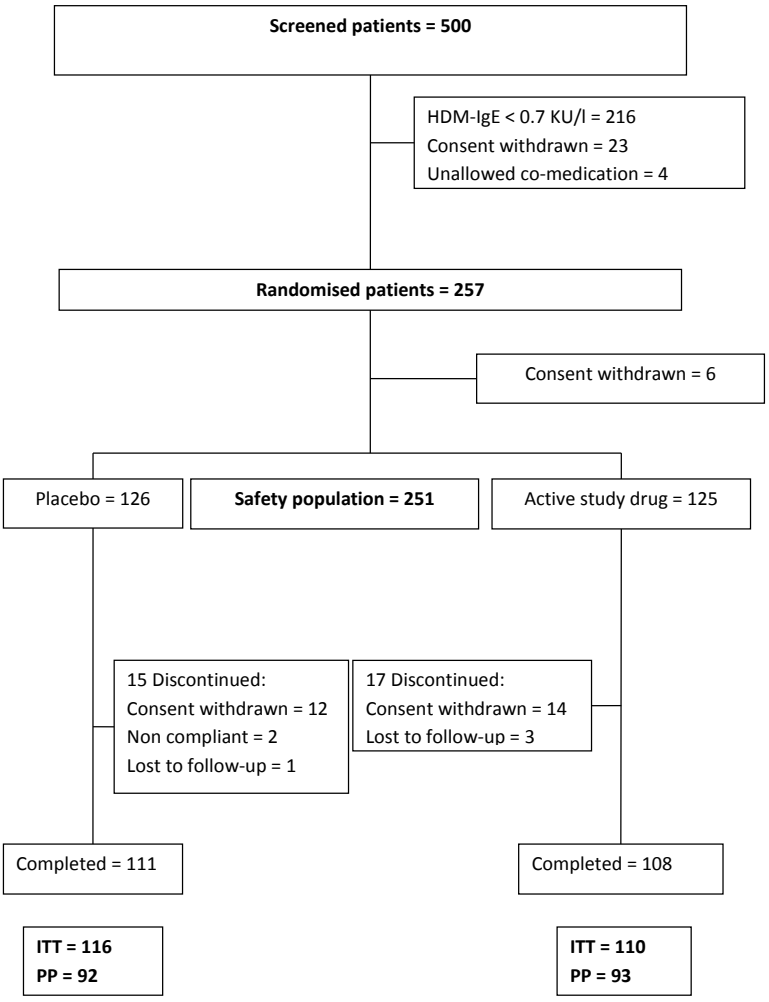

Figure 5.1: Flow chart of patient recruitment and follow-up.

The baseline demographic and clinical characteristics of each group are presented in Table 5.1. At baseline, all characteristics were well balanced between treatment groups; mean age of the patients was 11.7 years and 60% were boys. Mean nose symptom scores at baseline were 3.20 and 3.19 for the active study drug and placebo, respectively; 28% of children had a mean baseline score of 4 or higher, 17% had a baseline score of 5 or higher.

Only 19% of the patients were monosensitized. The total duration of treatment was 739 ± 61 days in the active study drug group and 735 ± 70 days in the placebo group. The proportion of patients taking ≥ 80% of the calculated dose was 81% in the placebo group and 86% in the active group (p= 0.38).

Table 5.1: Demographic characteristics of children in the study (ITT population)

	Active study drug (n=110)	Placebo (n=116)	All (n=226)
Male gender	67 (61%)	68 (59%)	135 (60%)
Age in years (mean ± SD)	11.8 ± 3.1	11.7 ± 2.9	11.7 ± 3.0
Age group			
6-11 years	54 (49%)	58 (50%)	112 (50%)
12-17 years	56 (51%)	58 (50%)	114 (50%)
Wheeze or dyspnea in past 12 months	60 (55%)	63 (54%)	123 (54%)
Sensitization status			
Monosensitized (%)	16 (15%)	28 (24%)	44 (19%)
Polysensitized (%)	94 (86%)	88 (76%)	182 (81%)
RAST HDM			
Class 2	18 (16%)	21 (18%)	39 (17%)
Class 3	18 (16%)	19 (16%)	37 (16%)
Class 4	25 (23%)	25 (22%)	50 (22%)
Class 5	35 (32%)	27 (23%)	62 (27%)
Class 6	14 (13%)	24 (21%)	38 (17%)
Retrospectivenose symptom score* **			
(mean ± SD)	6.9 ± 1.96	6.8 ± 2.09	6.8 ± 2.08
Baseline nose symptom score diary **			
(mean ± SD)	3.2 ± 1.96	3.2 ± 1.92	3.2 ± 1.94

* Retrospective nose symptom score during the last 3 months, based on telephone screening and should be at least 4 out of 12 for inclusion.

**Intensity of these symptoms (rhinorrhea, blocked nose, sneezing, itching) was subjectively assessed according to a grading scale: 0 = no complaints, 1 = minor complaints, 2 = moderate complaints and 3 = serious complaints; the maximum score was 12.

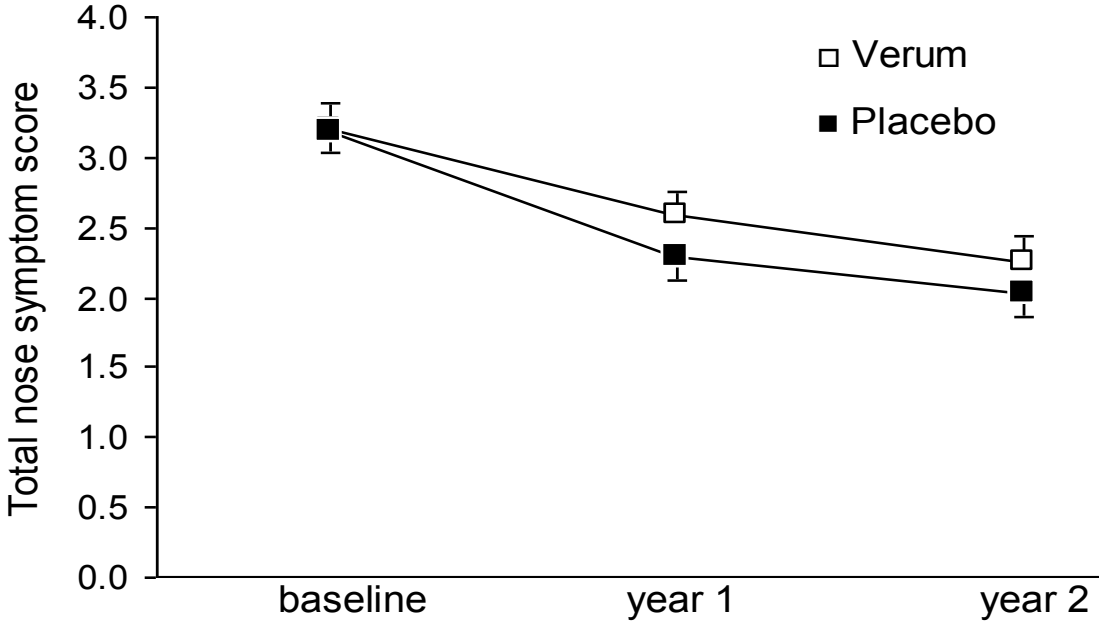

Figure 5.2: Mean daily total nose symptom score
Data shown are raw data. Error bars represent standard error of mean. The intensity of nose symptoms (rhinorrhea, blocked nose, sneezing, itching) were subjectively assessed according to a grading scale: 0 = no complaints, 1 = minor complaints, 2 = moderate complaints and 3 = serious complaints; the maximum score was 12.

Primary efficacy measure

After 2 years of treatment, the mean nose symptom score was reduced by 37% in the placebo group and by 26% in the active study drug group (Figure 5.2); in the ITT population the mean nose symptom score was 12% higher in the active study drug group than in the placebo group ((2.26 ± 1.84 and 2.02 ± 1.67; p=0.08) (Figure 5.2). The PP analysis of the primary endpoints showed no significant difference. Table 5.2 presents results of the repeated measurements ANOVA.

Secondary efficacy measures

At 2 year follow-up analysis of all secondary outcomes showed no significant differences between placebo and the active study drug for any of these parameters (Table 5.3). For separate symptoms no differences were found, except for dyspnoea/wheeze, an exploratory efficacy measure showing a significant difference after 2 years of treatment favouring the placebo group (p=0.010).

QoL did not differ between groups in total scores for the PRQLQ and AdolRQLQ (p=0.41 and p=0.84), or for the separate domains of these questionnaires.

The overall evaluation of the treatment effect by the patients did not differ between groups (Table 5.4, p=0.31).

Table 5.2: Results of analysis of Repeated measurements ANOVA of the mean daily total nose symptoms# (ITT analysis) after 2 years of treatment.

Total group-all covariates	**Effect**	**95% CI**	**p-value**
Treatment (Active study drug vs placebo)	0.117	-0.014 - 0.248	0.080
Age (per year)	-0.011	-0.030 - 0.008	0.245
Gender (female vs male)	-0.002	-0.123 - 0.119	0.974
Baseline mean symptom score at entry into study#	0.639	0.534 - 0.743	<0.001
House dust mite CAP class at entry into study(2 vs >2)	-0.082	-0.238 - 0.074	0.302
Cohort (1 vs 2)	-0.115	-0.236 - 0.006	0.063

Square root transformed mean scores

Table 5.3: Results of secondary outcomes (ITT analysis) after 2 years of treatment

mean ± SD	**Active study drug (n=110)**	**Placebo (n=116)**	**p-value**
Proportion of "well days" def1 *	0.22 ± 0.30	0.29 ± 0.35	0.24
Proportion of "well days" def 2**	0.49 ± 0.37	0.51± 0.40	0.75
Proportion of symptom free days def 1#	0.27 ± 0.31	0.34 ± 0.35	0.19
Proportion of symptom free days def 2##	0.25 ± 0.31	0.33 ± 0.35	0.18
Proportion of days with rescue medication	0.21 ± 0.35	0.26 ±0.40	0.17
Proportion of days with levocetirizine	0.11 ± 0.29	0.14 ± 0.33	0.71
Proportion of days with xylomethazoline nose	0.04 ± 0.12	0.03 ± 0.08	0.61
Proportion of day with levocabastine (eye)	0.004 ± 0.02	0.007±0.03	0.12
Total symptom score (nose and eye)	2.76 ± 2.42	2.59 ± 2.51	0.59
Eye symptom score	0.49 ± 0.77	0.57 ±1.03	0.94
Asthma symptoms *(exploratory outcome)*			
Dyspnoea/wheeze score	0.21 ± 0.46	0.11 ± 0.24	0.01
Dry cough score	0.15 ± 0.40	0.11 ± 0.25	0.19
PRQLQ (6-11 years)	0.93 ± 0.79 (n=51)	0.91 ± 0.69 (n=53)	0.41
AdolRQLQ (12-17 years)	0.93 ± 0.73 (n=58)	0.90 ± 1.00 (n=59)	0.84

* Well day defined as a day without nose symptoms and without rescue medication

** Well day defined as a day with minimal nose symptoms (max 2 points and per symptom not more than 1 point) and without rescue medication.

Symptom free day defined as a day with a nose total symptom score of 0.

Symptom free day defined as day with a combined nose and eye total symptom score of 0.

PRQLQ = Pediatric Rhinoconjunctivitis Quality of Life Questionnaire

AdolRQLQ = Adolescent Rhinoconjunctivitis Quality of Life Questionnaire

Table 5.4: Overall evaluation of the treatment effect

n (%)	Active study drug	Placebo	Total
Much worse, many more complaints	0 (0%)	2 (1.8%)	2 (0.9%)
Worse, more complaints	5 (4.8%)	2 (1.8%)	7 (3.3%)
No difference, similar complaints	39 (37.1%)	34 (31.2%)	73 (34.1%)
Slightly better, less complaints	35 (33.3%)	39 (35.8%)	74 (34.6%)
Much better, hardly any complaints	23 (21.9%)	30 (27.5%)	53 (24.8%)
No complaints any more	3 (2.9%)	2 (1.8%)	5 (2.3%)
Total	105	109	214

Table 5.5: Primary outcome: results of subgroup analyses after 2 years of treatment

Subgroups	Treatment effect	95% CI	p-value
Severity			
Baseline mean total nose symptom score <3	0.057	-0.122 - 0.236	0.53
Baseline mean total nose symptom score ≥ 3	0.180	-0.021 - 0.381	0.08
RAST class			
HDM CAP-class 2	0.125	-0.196 - 0.446	0.43
HDM CAP-class ≥ 3	0.125	-0.022 - 0.272	0.09
Sensitization			
Monosensitized	0.108	-0.260 - 0.477	0.56
Polysensitized	0.113	-0.032 - 0.259	0.13

Table 5.6: Number of patients with adverse events – safety population

		Active study drug (n=125)	Placebo (n=126)	Fisher exact test (two-sided; df=1)
Local	Oral pharyngeal irritation/swelling	14 (11.2%)	18 (14.3%)	X^2= 0.54 P = 0.57
	Gastro-intestinal complaints	85 (68.0%)	76 (60.3%)	X^2= 1.61 P = 0.24
General	Nasal complaints (rhinitis)	115 (92.0%)	118 93.7%	X^2= 0.26 P = 0.63
	Conjunctivitis	69 (55.2%)	82 65.1%	X^2= 2.56 P = 0.12
	Shortness of breath/cough	84 (67.2%)	87 (69.0%)	X^2= 0.10 P = 0.79
	Eczema/itch/rash	71 (56.8%)	82 (65.1%)	X^2= 1.81 p = 0.20
	Allergy (not specified)	75 (60.0%)	84 (66.7%)	X^2= 1.20 p = 0.30
Other		121 (96.8%)	121 (96.0%)	X^2= 0.11 p = 1.00

Subgroup analyses

None of the analyses showed a difference between the active study drug and placebo within any of the subgroups (Table 5.5). Reduction of the nose symptom score was larger in patients with a higher baseline score as compared to a low baseline score, but this difference was not significant (p=0.079).

Safety

A total of 251 patients were analysed for safety. The number of patients who reported adverse events was comparable between both groups (Table 5.6). No difference was seen in local oral pharyngeal irritation/swelling in both groups. The most commonly reported adverse event was nasal complaints. Nine patients, 6 on the active study drug and 3 on placebo reported a serious adverse event: generalized eczema; asthmatic complaints; hospitalization for appendicitis (2x); in hospital observation of asthma complaints (2x); planned surgery to replace brain drain; meniscus operation; and in hospital observation of constipation. None of these serious adverse events were considered to be related to the study drug.

Der p1 and Der f1 concentration

A mean concentration of 2.03 mcg/ml *Der p1* and no detectable *Der f1* was found in active study drug vials. No *Der p1* or *Der f1* was detected in the placebo vials. For the active study drug group, the total cumulative dose in a fully compliant patient over the 2-year period was estimated at 435 mcg *Der p1*.

DISCUSSION

This is the first large study conducted with house dust mite SLIT in allergic children in primary care. We found no significant effects of SLIT compared with placebo on our primary outcome, daily mean nose symptom score, or on the secondary endpoints, except for a significant worsening of one individual efficacy measure, dyspnea/wheezing, in the SLIT group.

Strengths

The study was designed to comply with current guidelines for the design, analysis and reporting of studies assessing the efficacy of immunotherapy.[31-34] It had a baseline assessment, was placebo-controlled, double-blind, randomized, had an adequate sample size, sufficient duration of treatment, patients were selected according to predefined clinical criteria, and the primary and secondary outcomes were clearly defined. The baseline assessment occurred between September and December; moreover, the out-

comes after 1 and 2 years of treatment were also assessed during this period, i.e. when house dust mites are most prevalent.[35-37]

The safety of SLIT in children has been confirmed in trials, systematic reviews and meta-analyses.[10-13,22,23] In our study, SLIT proved to be safe. We found a remarkable similarity in the proportion of patients with placebo and active study drug treatment reporting local symptoms. A possible explanation is that the activity of the allergen extract administrated was insufficient to generate local side effects.

The ARIA guidelines state that monosensitized subjects have more benefit from a single allergen SLIT treatment than polysensitized subjects.[5,6] In our study we included both mono- and polysensitized participants. About 81% of the participants were polysensitized. In contrast to our results, two recent trials suggested benefit of single-allergen SLIT in polysensitized patients.[38,39] Different pollen seasons can cause symptoms due to overlap, and various perennial allergens could be responsible for different outcomes in the evaluation of efficacy.[32] This is of importance in clinical practice because the majority of patients with allergy are polysensitized. Further studies are needed to establish whether single allergen SLIT is useful in polysensitized patients.

Our study had an unusually high compliance rate. Previous study showed that monitoring frequency is correlated with compliance.[40] We think that this may indeed have been the case in the present study, and that the high compliance was caused by the intensive monitoring scheme. Over the two years of treatment the total number of planned contacts was 13 home visits and 23 telephone calls, if possible all by the same research nurse.

Limitations

The cumulative dose in our study after 2 years of treatment was estimated at 435 mcg of *Der p1*, which seems relatively low compared to most other studies.27 This could be a possible explanation for the absence of an effect of SLIT compared to placebo, which has consequences for the generalizability of our findings.

A lack of similar studies makes it difficult to compare findings and doses between studies. If we compare HDM-SLIT studies with children and a diagnosis of allergic rhinitis (and/or asthma), different cumulative doses and different outcomes in efficacy are reported. Hirsch et al. reported a cumulative dose of 570 mcg for a duration of 1 year, concluding that SLIT over 12 months with the fivefold *Der p1* dose of subcutaneous IT was well tolerated, but no consistent clinical benefit or immunological change compared to placebo could be found.[41] Bahçeciler et al. reported a cumulative dose of 560 mcg over 6 months; their results suggest that SLIT may be a useful alternative or additional therapy in the treatment of children with asthma/rhinitis due to HDM.[42] Pham-Thi et al. performed a study in children with house dust mite-induced allergic asthma for 18

months with a cumulative dose of 6900 mcg Der. p1 and 14700 mcg Der. f1 and found no evidence for the efficacy of HDM-SLIT.[43]

Transparency in the total doses of major allergens and the immunologic activity of an allergen preparation should be encouraged and this information should be made available by manufacturers. Also, in most studies, failure to report the total dose of major allergens in standardized units hampers comparability.[44,45]

A relevant question is: was the disease severity of the present study population enough to allow detection of treatment effects? It is known that about 90% of the patients consulting a GP have moderate to severe disease.[46,47] In our population, the baseline symptom scores were considerably lower than the retrospective symptom scores assessed at inclusion. However, compared with other studies, our patients' symptom scores at baseline were similar or even higher.[43,48]

Most studies performed in referral centres reported symptom scores only after treatment [21,49]; the symptom scores in our study were comparable to these. Thus, there was substantial room for improvement and it is unlikely that the absence of effect can be explained by low initial symptom scores in the study population.

As all children were treated for two years, this should be sufficient to show an effect. Apart from the low SLIT dosage, mentioned above, another possible explanation for a lack of effect may be the regimen of twice weekly dosing during the maintenance phase. An animal study suggested that reducing dosing intervals may improve immunological outcomes.[50] However, the regimen in our study was in accordance with the manufacturer's guidelines and we adhered to these guidelines.

Calculation of mean scores in a fixed time period does not take into account the wide variation in day-to-day symptoms. Therefore, additional endpoints have been proposed to evaluate the efficacy of immunotherapy.[51] In the current study, however, primary and secondary outcomes did not differ between the active study drug and placebo group.

We found a statistically significant difference for the dyspnoea/wheeze score after two years of treatment in an exploratory analysis, favouring the placebo group. The absolute difference between group means was small, only 0.10 on a 0-4 point scale, hence the clinical relevance of this result is questionable.

In the Netherlands, patients are often referred to an allergologist for indication and treatment with SCIT or SLIT.[3,4] Recent articles also address the importance of primary care in the treatment and management of allergic rhinitis.[52-54] The World Allergy Organization proposed more collaboration between primary care and allergologists for an optimal delivery of SLIT in the community setting. GPs should be trained for the early detection, diagnosis, management and treatment of allergic disorders.[33] For these reasons, we considered it important to perform our study in a population that was seen in primary care. The effectiveness of SLIT for house dust mite allergy in such a population

is highly relevant, as marketing efforts of SLIT manufacturers have specifically targeted this group over the past decade.

Conclusion

HDM-SLIT with a relatively low dosage was not effective in this primary care population of children with allergic rhinitis. SLIT was in general safe and well tolerated.

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Chapter 6

Exhaled nitric oxide measures allergy not symptoms in children with allergic rhinitis in primary care

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ABSTRACT

Background

Allergic rhinitis and asthma are both inflammatory diseases and are often associated. Relationships between fractional exhaled nitric oxide (FeNO) and asthma, atopy and quality of life have been shown.

Aims

This study aimed to determine whether FeNO in children with allergic rhinitis (AR) (n=158) or combined allergic rhinitis and asthma (n=93) was associated with clinical symptoms, house dust mite (HDM)-specific IgE and rhinitis-specific quality of life, both cross-sectional and longitudinal.

Methods

Children with AR aged 6 to18 year (n=251) in primary care were assessed for FeNO, nasal symptom scores, asthma symptom scores, quality of life, and HDM specific IgE at baseline and 2 years later.

Results

We found similarly elevated FeNO in children with only AR and in those with combined AR and asthma. No correlations were found between FeNO and nasal or asthma symptoms and rhinitis-related quality of life. Longitudinal correlations were strongest for HDM specific IgE ($r= 0.91$, $p < 0.0001$).

Conclusion

FENO was similar in this selected group of children with AR with and without asthma in primary care and was unrelated to symptoms or quality of life in both groups. FENO is unlikely to be a useful biomarker of the clinical severity of upper or lower airway disease in primary care.

INTRODUCTION

Allergic rhinitis and asthma are both inflammatory diseases and are often associated. Asthma is present in 20–50% of patients with allergic rhinitis and allergic rhinitis exists in up to 80% of patients with asthma.[1] Both conditions are characterized by airway inflammation and blood eosinophilia.[2] Airway inflammation in asthma and allergic rhinitis involves release of biomarkers including nitric oxide.[3]

Fractional exhaled nitric oxide (FeNO) is a biomarker of eosinophilic airway inflammation.[4] The measurement of this gas is considered a reliable, non-invasive marker of eosinophilic airway inflammation, based on numerous studies that showed an association between the two.[5-7]

FeNO is produced by airway epithelial cells in response to inflammatory cytokines.[3,4] A recent review has shown that FeNO is increased in children with asthma and atopy.[8,9] A study found a lower quality of life in children with higher NO levels.[10] Other studies have addressed correlations between FeNO and total IgE or specific IgE to house dust mite and positive allergic skin tests.[11,12]

Single measurements of FeNO have been used to assess airway inflammation in asthma and atopy.[5,6] The usefulness of FeNO in the longitudinal assessment of for example asthma control has gained interest in the last couple of years.[13,14] The recent ATS guideline for the interpretation of FeNO for clinical applications stated that FeNO could be used as a biomarker that adds a new dimension to the traditional clinical tools in the assessment and management of airways diseases.[15]

The guidelines of the Allergic Rhinitis and its Impact on Asthma (ARIA) working group, in collaboration with the World Health Organization (WHO) stated that treatment of AR in children and adolescents should focus on achieving patients' well-being by minimizing symptoms and improving physical, psychological and social functioning.[1] Ideally, a combined strategy should be used to treat both upper and lower airway disease to improve patients' well-being.[1]

As part of a randomized double-blind placebo-controlled trial the present analysis gave us the opportunity to determine, both cross-sectionally and longitudinally, whether FeNO in children with allergic rhinitis only or with both allergic rhinitis and asthma was associated with nasal and asthma symptoms, rhinitis-related quality of life, house dust mite(HDM) specific IgE.

METHODS

Study design

The study was a randomized double-blind placebo-controlled trial, investigating the efficacy of 2 years of sublingual immunotherapy with SLIT with house dust mite allergen (SLIT-HDM) compared to placebo in 6 to 18-year-old children with HDM related allergic rhinitis in primary care. Within the framework of this study, patients were assessed for FeNO, nose symptom scores, asthma symptom scores and allergy related quality of life at baseline and after 2 years. Patients entered the study and started a 2-year treatment with verum or placebo. Written informed consent was obtained from parents of all children and assent from children aged 12-18 years. The study was approved by the Ethical Review Board of Erasmus MC University Medical Center Rotterdam. A detailed description of the study design has been published elsewhere.[16] For the trial, we included 251 children who were randomized to either SLIT or placebo treatment. Primary outcome parameter was the mean total nose symptom score (scale 0-12) during the autumn after two years of treatment.[17] Within this study population, there was no difference on study outcomes (proportion of symptom-free days, total mean eye symptom score, rhinoconjunctivitis specific quality of life i.e.) between the two groups after 2 years. This allowed us to pool the data of both study arms. The analyses described below were repeated for each experimental group separately, which yielded comparable results.

Children were subdivided into those with allergic rhinitis only and those with both allergic rhinitis and asthma.

Patients

Children aged 6-18 years with at least a 1-year history of allergic rhinitis were invited by their general practitioner (GP) for this study. Children were screened for the following predefined criteria: IgE antibodies ≥0.7 kU/l to house dust mite (CAP-Phadiatop®, Pharmacia Diagnostics AB, Uppsala, Sweden); did not use nasal steroids in the month before start of baseline measurements; had a retrospective nose symptom score of at least 4 out of 12 points during the last 3 months; and provided written informed consent. Patients were excluded when they had been treated with immunotherapy in the previous 3 years; had severe asthma; had a sensitization to pets present at home at entry in the study (IgE antibodies ≥0.7 kU/l); or had a planned surgery of the nasal cavity.[16]

Asthma

The presence of asthma was assessed with the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [18] in case of a positive answer to the following question: "Did you / your child ever have asthma?"

Nasal symptom score in diary

Nasal symptoms were scored for 4 nasal symptoms (rhinorrhea, blocked nose, sneezing, itching) at baseline and after 2 years. The intensity of these symptoms was subjectively assessed according to a grading scale from 0-3 (0 = no complaints, 1 = minor complaints, 2 = moderate complaints and 3 = serious complaints); the maximum score was 12. The scores were assessed daily by the patient or parents and recorded in a diary. The period of measurement was 1 month at baseline at the beginning of the trial and 3 months after 2 years, both in the period September through December. The nasal score is a cumulative mean daily nose symptom score measured in a period of 3 months.

Asthma symptom score in diary

Wheezing/dyspnea and dry cough during the night were scored in a diary. The intensity of these two symptoms was assessed according to the same grading scale as for nasal symptoms, the maximum score was 6.

House dust mite-specific IgE

Serum IgE antibodies to Dermatophagoides pteronyssinus were determined at baseline and year 2 using the CAP-Phadiatop®,(Pharmacia Diagnostics AB, Uppsala,Sweden), according to the manufacturer's instructions. Allergen-specific IgE values of 0.7 kU/l (class II) or greater were considered positive.

Quality of life

Rhinoconjunctivitis specific quality of life was assessed at baseline and after two years. We used the Dutch version of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). This questionnaire was originally developed and validated in pediatric (6-11 years) and adolescent (12-17 years) patients (PRQLQ and AdolRQLQ).[19,20] The questionnaire used at baseline was repeated after 2 years. As we used two different Quality of Life questionnaires (for children of 6-11 year and children 12-17 years), we standardized both data by subtracting the mean group score and dividing by the mean standard deviation, enabling us to combine the data for both age groups.

FeNO

FeNO was single measured at baseline and after 2 years using a hand-held portable nitric oxide analyzer (NIOX MINO, Aerocrine AB, Solna, Sweden). Participants were asked to inhale to total lung capacity and then exhale through the NIOX MINO at a mouth flow rate of 50 ml/s over 10 seconds as per guideline recommendation, assisted by visual and auditory cues. The measurement range of NIOX MINO is 5 to 300 ppb.[5,6]

Statistical analyses

Analysis was performed by means of SPSS 17 for Windows (SPSS Inc, Chicago, IL, USA). Data from the total group of children was subdivided into children with allergic rhinitis only and children with allergic rhinitis and asthma. The nose and asthma symptom sum scores and house dust mite specific IgE values at baseline and after 2 years were square root transformed in order to get approximately normal distributions. FeNO measurements were ln-transformed for analysis in order to get a normal distribution. The strengths of cross-sectional correlation between FeNO, nasal and asthma symptoms, rhinitis-related quality of life, house dust mite-specific IgE and allergy skin testing was assessed by using the Pearson correlation coefficient. For the purpose of the analysis, correlation coefficients ≥0.8 were considered very strong, from 0.6 to 0.79 considered strong, from 0.4 to 0.59 considered moderate, from 0.2 to 0.39 considered weak, and <0.2 considered very weak.[21] The assessment of the longitudinal correlations between baseline and 2 years for FeNO levels, nose and asthma symptom, rhinitis-related quality of life and house dust mite specific IgE were done by estimating linear regression models. A 2-sided P value of < 0.05 was regarded as statistically significant.

RESULTS

Demographic and clinical characteristics

The study population consisted of 251 children. The demographic and clinical characteristics of the groups at baseline are presented in Table 6.1-6.3. Table 6.1-6.3 also shows the patients divided into two subgroups. There were 158 children with only allergic rhinitis (AR), and 93 children with allergic rhinitis and asthma (AR and asthma). Fifty-nine percent were boys. The mean age of all patients was 11.8 years and 79% of the patients were multisensitized. (Table 6.1)

Table 6.1: General characteristics of the population subdivided on the basis of only allergic rhinitis (AR) or allergic rhinitis and asthma

	AR only (n=158)	AR and asthma (n=93)	P-value	Total (n=251)
Gender (Male %)	89(56%)	60 (65%)	0.2	149 (59%)
Age (y) mean ± SD	12 ± 3.1	11.3 ± 3.0	0.09	11.8 ± 3.0
Wheeze or dyspnea in past 12 months YES	62 (39%)	74 (80%)	<0.001	136 (54%)
Polysensitized (%)	121 (77%)	77 (83%)	0.3	198 (79%)

Table 6.2: Symptoms and rhinitis related quality of life of the population subdivided on the basis of only allergic rhinitis (AR) or allergic rhinitis and asthma

	AR only (n=158)	AR and asthma (n=93)	P-value	Total (n=251)
Nasal symptoms at baseline* mean± SD	3.2 ± 1.8 (n=158)	3.2 ± 1.9 (n=93)	0.5	3.2 ± 1.9 (n=251)
Nasal symptoms year 2* mean± SD	2.1 ± 1.7 (n=136)	2.2 ± 1.8 (n=78)	0.8	2.1 ± 1.8 (n=214)
Asthma symptoms at baseline** mean± SD	0.5 ± 0.9 (n=158)	0.9 ± 0.9 (n=93)	0.001	0.6 ± 0.9 (n=251)
Asthma symptoms year 2** mean± SD	0.2 ± 0.6 (n=136)	0.4 ± 0.8 (n=78)	0.02	0.3 ± 0.7 (n=214)
QoL Juniper (standardized) at baseline*** mean± SD	-0.1 ± 0.9 (n=146)	0.2 ± 1.1 (n=86)	0.012	0.0 ± 1.0 (n=232)
QoL Juniper (standardized) year 2*** mean± SD	0.0 ± 1.0 (n=133)	0.1 ± 1.0 (n=78)	0.5	0.0 ± 1.0 (n=211)

*The intensity of these symptoms (rhinorrhea, blocked nose, sneezing, itching) were subjectively assessed according to a grading scale: 0 = no complaints, 1 = minor complaints, 2 = moderate complaints and 3 = serious complaints; the maximum score was 12.
** The intensity of these symptoms (wheezing/dyspnea and dry cough during the night) was subjectively assessed according to a grading scale: 0 = no complaints, 1 = minor complaints, 2 = moderate complaints and 3 = serious complaints; the maximum score was 6
*** standardized Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) 6-11 year and Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (AdolRQLQ) 11-17 year

Table 6.3: Measurements of the population subdivided on the basis of only allergic rhinitis (AR) or allergic rhinitis and asthma

	AR only (n=158)	AR and asthma (n=93)	P-value	Total (n=251)
FeNO in ppb at baseline median (IQR)	34 (16-55) (n=151)	36 (18-55) (n=91)	0.94	35 (17-55) (n=242)
FeNO in ppb year 2 median (IQR)	34 (19-63) (n=136)	34 (19-59) (n=77)	0.78	34 (19-61) (n=213)
HDM# specific IgE(kU/l) at baseline mean± SD	40.2 ± 36.3 (n=158)	55.0± 37.2 (n=93)	0.002	45.7 ± 37.3 (n=251)
HDM# specific IgE(kU/l) year 2 mean± SD	41.5 ±35.9 (n=133)	58.4 ± 33.8 (n=77)	0.001	47.7± 36.0 (n=210)

house dust mite

Nasal symptoms, asthma symptoms and rhinitis specific quality of life

Mean nasal symptom score as assessed by diary at baseline was 3.2 and at year 2 2.1. Mean asthma symptom score was 0.6 at baseline and 0.3 at year 2. Children with combined AR and asthma scored significantly higher on asthma symptoms (Table 6.2), compared to those with AR only. Children with AR only had significant lower scores on

the RQLQ, indicating a better rhinitis specific quality of life compared to children with both AR and asthma at baseline (p=0.01) and at 2 years (p=0.02). (Table 6.2)

FeNO, house dust mite specific IgE

FeNO was similarly elevated in children with AR with and without asthma at baseline and after 2 years (median FeNO levels range between 34-36 ppb, Table 6.3). Mean HDM specific IgE was 45.7 kU/l at baseline and 47.7 kU/l at year 2. Children with AR and asthma had significant higher levels of house dust mite-specific IgE in both years, compared to children with only AR (baseline, 55.0 kU/l , year 2, 58.4 kU/l).

Cross-sectional correlations between FeNO, nasal and asthma symptoms and rhinitis-related quality of life

No or very weak correlations, ranging between 0.147 and 0.192, were found between FeNO levels and nasal symptoms, asthma symptoms or quality of life in both groups in both years.

Cross-sectional correlation between FeNO and HDM specific IgE

A moderate cross-sectional correlation was found between FeNO levels and house dust mite-specific IgE at baseline ($r= 0.404$; $p < 0.0001$) and a weak correlation in year 2 ($r= 0.366$; $p < 0.0001$) in the total group, as demonstrated in Figure 6.1. Similar results were obtained for children with allergic rhinitis only: moderate correlations were found between house dust mite-specific IgE and FeNO at both years (baseline, $r = 0.441$, $p < 0.0001$; year 2, $r = 0.448$, $p < 0.0001$). There was also a weak correlation between house dust mite-specific IgE and FeNO in children with allergic rhinitis and asthma. However, this correlation was only seen at baseline ($r = 0.349$, $p = 0.001$).

FeNo values, nasal and asthma symptoms, rhinitis specific quality of life and house dust mite specific IgE determined longitudinally at baseline and year 2

The longitudinal correlation between FeNO values of year 0 and year 2 were moderate. ($r= 0.597$, $p < 0.0001$). (Figure 6.2) Moderate to strong correlations were seen for nasal symptoms, asthma symptoms and rhinitis specific quality of life, shown in Table 6.4. A very strong correlation was seen baseline for house dust mite specific IgE at baseline and year 2 ($r= 0.911$, $p < 0.0001$). Similar correlations were seen for FeNO, nasal and asthma symptoms, rhinitis specific quality of life and house dust mite specific IgE for children with only AR and combined AR and asthma at baseline and year 2, as shown in Table 6.4.

Figure 6.1 A and B: Cross-sectional correlations between FeNO values and house dust mite specific IgE(total group n=251)

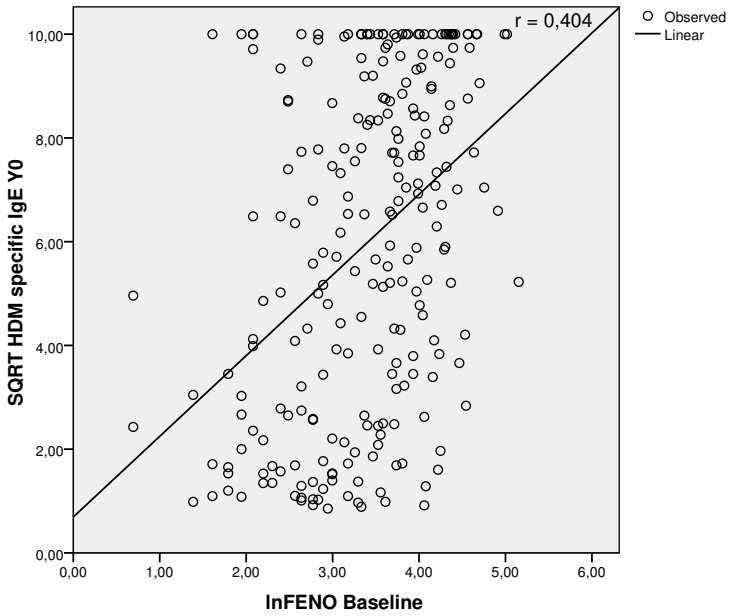

Figure 6.1A: Total group baseline (n=251)
P<0.0001

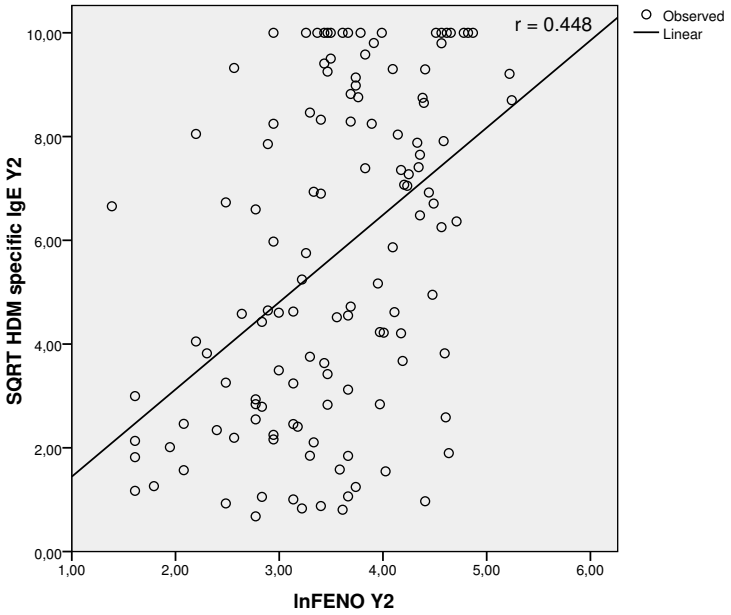

Figure 6.1B: Total group year 2 (n=251)
P<0.0001
HDM= house dust mite
SQRT= square root transformed
Ln= ln-transformed

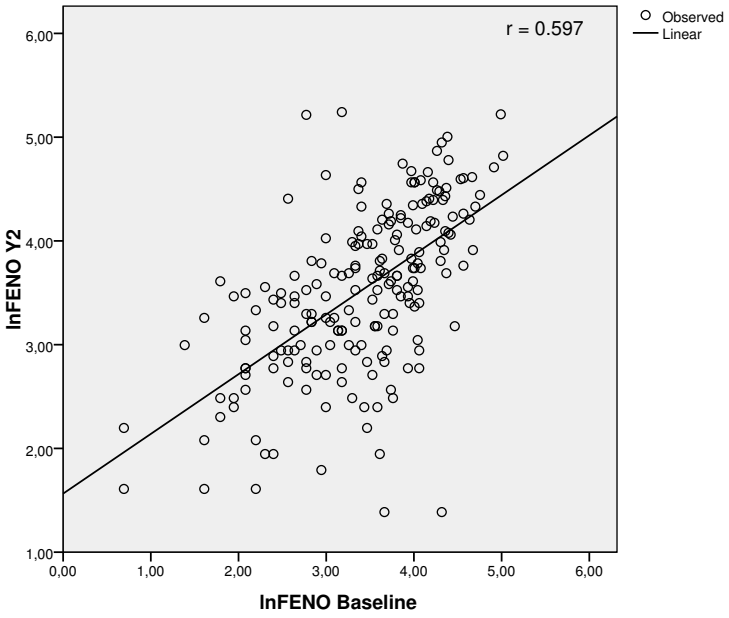

Figure 6.2: Longitudinal correlation between FeNO determined at baseline and two years later (total group n=251)
P<0.0001

Table 6.4: Correlation between FeNO values nasal symptoms, asthma symptoms, rhinitis specific quality of life and HDM specific IgE determined at baseline and two years later (Y2)

	Total group (n=251)	AR only (n=158)	AR and asthma (n=93)
FeNO levels baseline-Y2	r = 0.597*	r = 0.642*	r = 0.502*
Nasal symptoms baseline-Y2	r = 0.611*	r = 0.614*	r = 0.607*
Asthma symptoms baseline-Y2	r = 0.564*	r = 0.507*	r = 0.575*
Rhinitis specific Quality of Life baseline-Y2	r = 0.442*	r = 0.405*	r = 0.505*
HDM# specific IgE baseline-Y2	r = 0.991*	r = 0.913*	r = 0.894*

*p<0,0001
house dust mite

DISCUSSION

Main findings

In this primary care pediatric population, which were all children with allergic rhinitis who had a positive specific IgE test to HDM, we found similarly increased levels of FeNO in children with AR and combined AR and asthma, as compared to reference values for healthy children.[6,15] FeNO was not associated with reported nasal and asthma symptoms, nor with allergic rhinitis disease-specific quality of life in children with allergic rhinitis and house dust mite allergy. The longitudinal correlations of FeNO, nasal and

asthma symptoms, rhinitis specific quality of life and house dust mite specific IgE were moderate to strong.

Interpretation of findings in relation to previously published work

Several studies demonstrated an association between FeNO levels and respiratory symptoms in children.[22,23] Steerenberg and colleagues reported that wheezing, nasal discharge and conjunctivitis were positively associated with FeNO levels in atopic children.[22] However, other studies failed to find a correlation between FeNO and symptoms.[11,24] Similarly, we found no correlation between FeNO and reported nasal and asthma symptoms. These discrepancies may be explained by the different definitions of for example nasal or asthma symptoms, the definition of allergic rhinitis and the heterogeneity of the study populations. Also, symptoms depend not only on inflammation but on multiple other mechanisms, including the level of perception, and this would obscure any relation with FeNO. It would be advantageous if investigators used standardized definitions and data collection methods for assessing asthma symptom severity or wheeze.[25]

In accordance with others, we found no association between FeNO and the quality of life of children with allergic rhinitis.[26] However, another study did report a correlation.[10] Probably, this apparent discrepancy may be explained by differences in study population and using different quality of life questionnaires. On the other hand, in this study we show that children with AR and asthma had lower rhinitis specific quality of life score (in addition to asthma symptoms) than children with AR alone, which could be interpreted as more active airway inflammation in these children.

Several studies demonstrated a positive association between FeNO and total IgE, specific IgE for house dust mite.[11,12] The present study also shows a moderate association between FeNO levels and house dust mite-specific IgE in children with allergic rhinitis and with both allergic rhinitis and asthma. Two studies found that total and HDM-specific IgE levels and blood eosinophilia showed moderate-to-strong correlations with FeNO.[27,28] This result suggests that specific IgE-dependent mechanisms are involved in eosinophilic inflammation of the airway in atopic and asthmatic children or even in children without allergic sensitization be present.[27,28] Leuppi et al. have shown that positive skin prick tests for house dust mite were associated with raised FeNO.[9] Cardinale and coworkers concluded that FeNO levels correlated better with total IgE than with positive skin prick tests in children with mild intermittent asthma or allergic rhinitis. However, both markers correlated with FeNO.[12] These studies indicate that FeNO is a marker of inflammation triggered by allergen exposure.

There is controversy whether atopy rather than asthma would explain elevated FeNO levels. The increase of FeNO in non-asthmatic individuals suggests that FeNO reflects allergic inflammation of the airways, depending on the degree of atopy.[29] Malmberg [30]

suggested that FeNO is a marker of eosinophilic inflammation in asthma, irrespective of the presence of atopy. Franklin et al. stated that elevated FeNO could be associated with atopy but not with doctors diagnosed asthma.[24] Other studies did not find differences in FeNO levels between patients with rhinitis or asthma.[31,32] In our study, we also did not find differences in FeNO between children with allergic rhinitis or allergic rhinitis and asthma. When assessing the relationship between FeNO and asthma or atopy, one must consider that FeNO is a marker of airway inflammation. Asthma and AR are both inflammatory diseases of the airways, and lower airways may exhibit allergic inflammation without symptoms, that could be responsible for a possible FeNO variation. Also atopy status [9] and allergen exposure [33] may affect FeNO levels.

Changes in FeNO measured over time may better reflect underlying changes in airway inflammation than single measurements.[15] Roberts et al indicated that levels of FeNO could provide better clinical information when compared with a child's previous FeNO than when compared with a population based normal range.[13] Indeed, Van der Valk et al. showed that repeated FeNO measurements could predict asthma exacerbations in children with a lag of 1-2 weeks.[14] Our time interval of 2 years may be too long to reflect underlying changes in airway inflammation. Also children face major changes in physical development during two years, which could have influenced the natural course of asthma, as well as FeNO levels.

Implications for future research, policy and practice

The recent ATS guideline for the interpretation of FeNO for clinical applications stated that FeNO could be used as a biomarker that adds a new dimension to the traditional clinical tools in the assessment and management of airways diseases.[15] Our results suggest that the role of FeNO measurements in a primary care population of atopic children deserves special attention. We propose that studies are needed how to interpret FENO measurements in primary care.

Strengths and limitations of this study

We examined a large group of children with allergic rhinitis in primary care, to see if FeNO could be a useful measure of upper or lower airway disease severity in in children with mild to moderate disease. In the Netherlands, the majority of patients with allergic rhinitis are treated by primary care physicians. Therefore, we considered it important to perform this analysis in this population. Some aspects of this study may have affected our results. First, the definition of asthma was based on questionnaire data. The considerable prevalence of asthma symptoms without a previous doctor diagnosis of asthma may indicate undiagnosed asthma. It might be that a definition based on a doctors' diagnosis of asthma [24] or based on objective measures such as reversibility to beta-2-agonist, lung function or bronchial hyperresponsiveness would be more accurate. However, this

higher specificity would unavoidably lead to a much lower sensitivity and loss of many cases. We did not perform multivariate analyses to control for potential confounding effects of inhaled corticosteroids (ICS) treatment or indoor allergen exposure associated with FeNO, as we did not have these data for all children. Both aspects could have consequences for the generalizability of our findings but are probably not differential and hence it is unlikely that this affects our findings.

Conclusions

In conclusion, FeNO was similar in this selected group of children with AR with and without asthma in primary care and was unrelated to symptoms or quality of life in both groups. FeNO was related to specific IgE to HDM at baseline and at two years. FeNO is unlikely to be a useful measure of the clinical severity of upper or lower airway disease in children in primary care.

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Chapter 7

Sensitization patterns and association with age, gender and clinical symptoms in children with allergic rhinitis in primary care

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ABSTRACT

Background

Polysensitization is a frequent phenomenon in patients with allergic rhinitis. However, few studies have investigated the characteristics of polysensitized children, especially in primary care.

Objective

This analysis describes the patterns of sensitization to common allergens and the association with age, gender and clinical symptoms in children in primary care who are diagnosed with allergic rhinitis.

Methods

In a cross-sectional study, children with allergic rhinitis aged 6 to18 years (n=784) in primary care were assessed for age, gender, specific IgE (type and number of sensitizations), nasal and eye symptom scores.

Results

In 699/784 children (89%) a positive IgE test for one or more allergens was found. Polysensitization (≥ 2 sensitizations) was found in 69% of all children. Sensitization was more common in children aged 9 to 13 than in younger children (5 - 8 year) (p=0.03). Mono,- and polysensitization was not significantly different in both girls and boys. Severity of clinical symptoms did not differ between polysensitized children and monosensitized children, but the symptoms were significantly lower in non-sensitized children.

Conclusion

Polysensitization to multiple allergens occurs frequently in children with allergic rhinitis in general practice. Overall, clinical symptoms are equally severe in polysensitized children as in monosensitized children. Treatment decisions for allergic rhinitis should be made on the basis of a clinical history and allergy testing.

INTRODUCTION

Allergic rhinitis (AR) is an inflammatory disease of the nasal membrane which is characterized by symptoms such as sneezing, rhinorrhea, nasal congestion and nasal itching. It is often associated with eye symptoms such as tearing, redness and itching. AR is caused by sensitization to one or more aeroallergens. It is a common chronic disorder among children [1,2] and can significantly impair quality of life. It is associated with a number of common co-morbidities, including asthma, sinusitis and otitis media.[1,2] Early intervention might minimize the likelihood of progression to more severe allergic diseases in children, including asthma.[3] Polysensitization might be a phenomenon that is clinically relevant. Several studies have pointed out that up to 90% of patients are polysensitized.[4,5] Only a few studies have addressed and discussed polysensitization in children and have been performed in referral centers. Kim et al. concluded that in polysensitized children the symptom scores and levels of total IgE were higher compared to the monosensitized group of children.[6] A study with both adults and children indicated that polysensitized individuals have atopic disease with a more severe course.[5] Another study showed that polysensitization was associated with a significant poorer quality of life.[7] More recently, Baatenburg de Jong and colleagues concluded that polysensitization is common in school-aged children, in particular in boys.[8]

Persisting or recurrent symptoms of rhinitis can occur in both allergic and non-allergic disorders, and this overlap can confound the diagnosis and therapy.[9,10,11] Assessment of allergic sensitization is important in the diagnosis and management of allergic disease throughout childhood, because it enables tailored allergen-specific avoidance measures, allergen-specific treatment, relevant pharmacotherapy and can identify infants at increased risk for developing allergic diseases later in life.[10,11] In many European counties, such as the United Kingdom and The Netherlands, the majority of patients with allergic rhinitis and asthma are diagnosed and treated by primary care physicians.[12,13]

The aim of the current study is to describe the patterns of sensitization to common allergens and the association with age, gender and clinical symptoms in children with allergic rhinitis in primary care, which were eligible for a study investigating the efficacy of SLIT with either grass pollen allergen or house dust mite allergen.

METHODS

Study design

Cross sectional data of two randomized double-blind placebo-controlled studies, investigating the efficacy of SLIT with either grass pollen allergen or house dust mite allergen in 6 to 18-year-old children with allergic rhinitis and a proven grass pollen or house dust

mite (HDM) allergy in primary care were used. The present study used data from the recruitment phase. Written informed consent was obtained from parents of all children and from children aged 12-18 years. The study was approved by the Ethical Review Board of Erasmus MC University Medical Center Rotterdam. Detailed descriptions of design and results of both studies have been published elsewhere and are summarized below.[14-16]

Recruitment

General practitioners in the south-western part of the Netherlands selected children aged 6 to 18 years in their computerized patient records with either a diagnosis of hay fever/allergic rhinitis (ICPC R97) or with relevant medication use (i.e. antihistamines for systemic use; nasal corticosteroids; topical decongestants; topical antihistamines). After telephone screening a house visit took place for those who agreed (children / parents) for further participation. During the telephone screening, children who had no (or only short) history of allergy or who had a low symptom score were excluded.[14,15]

During the house visit, which in both studies took place in September-October, symptom scores were recorded and a blood sample was collected by a research assistant.

Symptom scores

- Rhinitis symptom scores: the intensity of the symptoms 'rhinorrhea', 'blocked nose', 'sneezing', 'itching' was subjectively assessed according to a grading scale from 0 to 3 (0 = no complaints, 1 = minor complaints, 2 = moderate complaints and 3 = serious complaints). The maximum score was 12.
- Conjunctivitis symptom score: the intensity of this symptom 'itching eyes' was subjectively assessed according to a grading scale from 0-3 as described above, with a maximum of 3.
- In the grass pollen study, the participants scored their nose and eye symptoms during the previous grass pollen season (i.e. May-August) and the last week. In the house dust mite study the children scored their symptoms during the last three months (i.e. July-September or August-October) and during the last week.

Allergen-specific IgE

A blood sample was collected for the assessment of allergen specific IgE to grass pollen, birch pollen, HDM, cat dander; and pets if present at home (RAST CAP-Phadiatop®, Pharmacia Diagnostics AB, Uppsala, Sweden). Sensitization to an allergen was defined as positive when allergen-specific IgE levels were 0.35 kU/L or higher (≥ class 1).[1,2]

Mono- and polysensitization

Subjects sensitized to only one tested allergen were defined as monosensitized, and those sensitized to two or more tested allergens, were defined as polysensitized. For polysensitized children, we distinguished sensitization patterns of two, three and four or more (maximum seven) sensitizations.

We analyzed the different perceptions of nasal and eyes symptoms in:
- non-sensitized children
- children with a grass pollen sensitization but not a HDM sensitization
- children with a HDM sensitization, but not a grass pollen sensitization
- children with both a grass pollen and HDM sensitization.

In the grass pollen study, 307 children were visited and in the house dust mite study 500 children (a total of 807 children). For the present analysis, we only included children who fulfilled the criteria of completely recorded symptom scores (nasal and eye) and an analysed blood sample for allergen specific IgE test (irrespective of the result).

Statistical analyses

Statistical analysis was performed with SPSS 18 for Windows (SPSS Inc., Chicago, IL, USA). The differences between means were analysed by the independent- samples t-test, differences between proportions were analysed by chi-square tests.

RESULTS

Demographic and clinical characteristics

The study population consisted of 784 children. The demographic and clinical characteristics of the groups are presented in Table 7.1. Fifty-seven percent were boys. The mean age of all patients was 12.2 years. The mean nasal symptom score was 6. The mean eye symptom score over the last three months was 1.4.

Sensitization patterns, age groups and gender

Sensitization to an allergen was found in 89% of the patients (n=699). Table 7.1 shows that polysensitization was found in 69% of all children (n=784). The mean number of positive tested sensitization was two. Sensitization to two tested allergens was found in 298 out of 784 children (38%), three positive IgE tests for specific allergens were found in 166 children (21%) and sensitization to four or more allergens in 174 children (22%). The mean levels of specific grass pollen IgE and house dust mite IgE in children who are sensitized, were respectively 41.8 kU/L and 26.9 kU/L (Table 7.1).

Table 7.1: General characteristics of the population

	Total (n=784)
Gender (Male %)	57%
Age (y) mean ± SD	12.2 ± 3.1
Age group (n, %)	
5-8 y	102 (13%)
9-13 y	373 (48%)
14-17 y	308 (39%)
Nasal symptoms (past season for GP / last 3 months for HDM	6.0 ± 2.4
Nasal symptoms past week	3.8 ± 2.8
Eye symptom past 3 months	1.4 ± 1.1
Eye symptom past week	0.6 ± 0.8
No sensitization	85 (11%)
Monosensitization	161 (20%)
Polysensitization	538 (69%)
Sensitization to *	
Grass pollen	587 (75%)
House dust mite	500 (64%)
Birch pollen	363 (46%)
Cat	229 (29%)
Grass pollen specific IgE (KU/l) mean ± SD*	41.8 ± 40.9
House dust mite specific IgE (KU/l) mean ± SD*	26.9 ± 35.0
Tree pollen specific IgE (KU/l) mean ± SD*	13.2 ± 26.7
Cat specific IgE (KU/l) mean ± SD*	2.3 ± 7.7
Total number of allergy tests for other pets at home	507
Sensitization to other pets at home * (n, %)	126
Dog	85 (67%)
Rabbit	19 (15%)
Other	22 (18%)

* IgE antibodies ≥0.35kU/l

Table 7.2: Co-sensitization patterns in children to one or more allergens

Co-sensitization to → In children sensitized to↓	House dust mite* n (%)	Grass pollen* n (%)	Birch pollen* n (%)	Cat dander* n (%)
House dust mite* (n=500)		395 (79%)	245 (49%)	202 (40%)
Grass pollen* (n=587)	394 (67%)		352 (60%)	213 (36%)
Birch pollen* (n=363)	249 (69%)	352 (97%)		165 (45%)
Cat dander* (n=229)	202 (88%)	213 (93%)	165 (72%)	

*IgE antibodies ≥0.35 kU/L

Example: 500 children were sensitized to house dust mite; 395 (79%) of these 500 children were also sensitized to grass pollen, 245 (49%) to birch pollen. Sensitization to birch pollen was found in 363 children, 249 of them (69%) were co-sensitized to house dust mite, etc

The co-sensitization patterns to grass pollen, house dust mite, birch pollen and cat dander are presented in Table 7.2. In children sensitized to house dust mite, 79% had also a co-sensitization to grass pollen. In children sensitized to birch pollen, 97% had a co-sensitization to grass pollen. In children sensitized to cat dander, 88% had a co-sensitization to house dust mite and 93% a co-sensitization to grass pollen.

The percentage of children in each sensitization group for the different age groups is presented in Figure 7.1A. Sensitization was more common in children aged 9-13 year compared to younger children (5-8 year) (p=0.03). The difference between the oldest age group (14-17 year) and the youngest age group did not reach statistical significance (p=0.08). This was also seen between children aged 9-13 year and children in age group 14-17 year (p=0.88).

The gender distribution in the sensitization groups is shown in Figure 7.1B. The sensitization pattern was not significantly different between girls and boys (p=0.11).

Figure 7.1A and B: Distribution of sensitization patterns by age group (A) and gender (B)

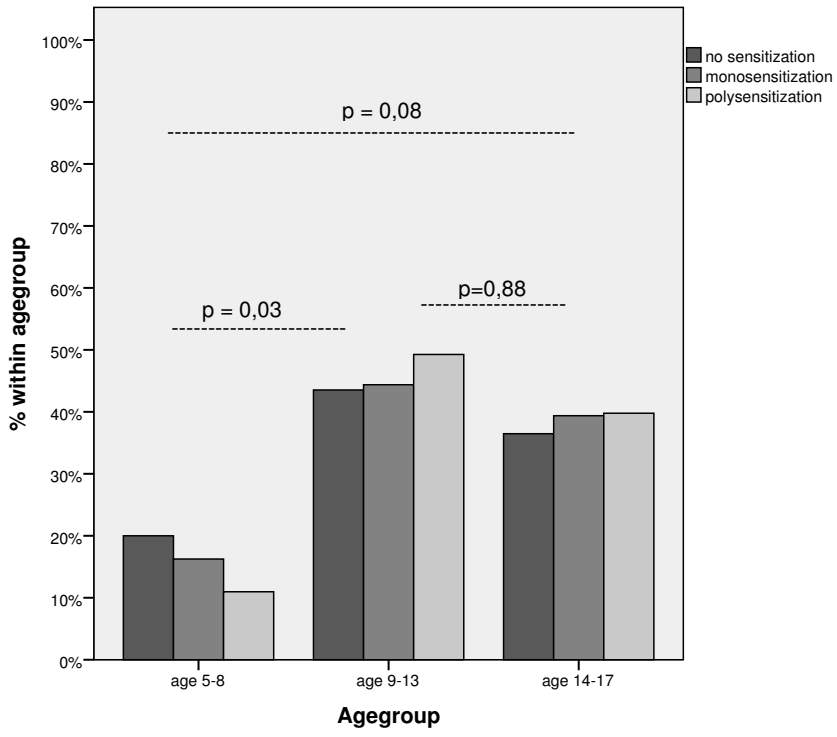

Figure 7.1A: Percentage of children within each age group for each category of sensitization

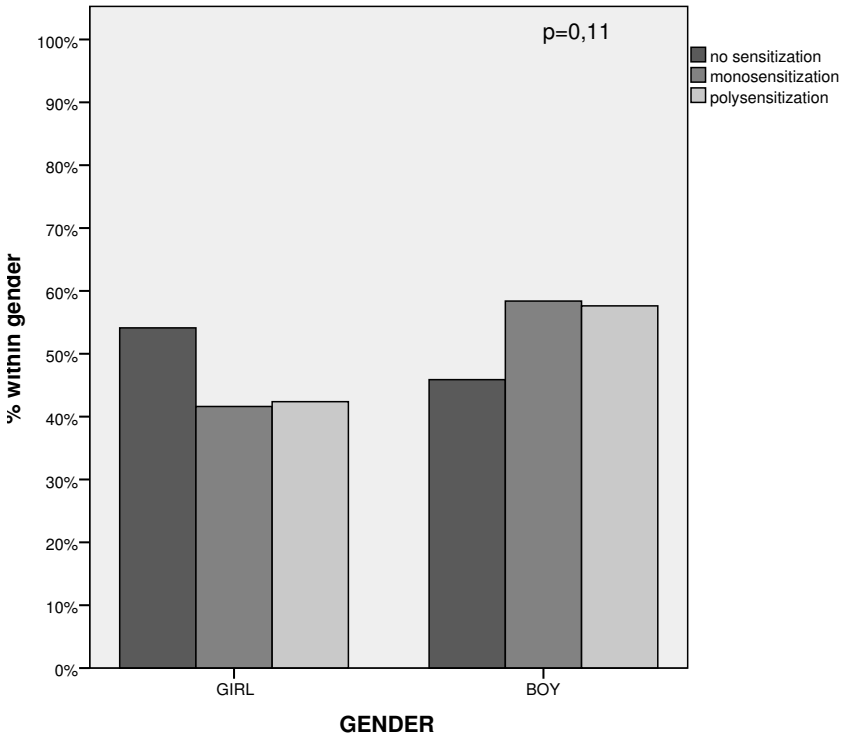

Figure 7.1B: Percentage of girls and boys within each sensitization category

Self-reported nasal and eye symptom scores

The mean nasal symptoms during the last three months was significantly lower in non-sensitized children compared to mono- and polysensitized children (Figure 7.2A; p = 0.001). This was also seen for the mean eye symptom score during the last three months in non-sensitized children compared to mono- and polysensitized children (Figure 7.2B; p<0.0001). There was no significant difference between mono- and polysensitized children in nasal and eye symptoms.

As shown in Figure 7.2C the perceived severity of nasal symptoms during the last three months was significant higher in children with a HDM or grass pollen sensitization or a combination of both allergens compared to children without a sensitization (p<0.001 and p = 0.001). There was no significant difference between children sensitized to HDM or grass pollen only and children with a sensitization to both allergens.

The perceived severity of itching eyes symptoms during the last three months was significantly higher in children with a grass pollen sensitization (without a HDM sensitization) compared to children with only a HDM sensitization (without a grass pollen sensitization) or children with sensitization to both grass pollen and HDM (p< 0.001 and p=0.008). Children with sensitization to both grass pollen and HDM reported higher eye symptoms to those with HDM sensitization only (p=0.009) (Figure 7.2D). Compared to non-sensitized children, the perceived severity of itching eye symptoms during the last

Figure 7.2 A – D: Perception of nasal and eye symptom score in children with different sensitization patterns during last 3 months

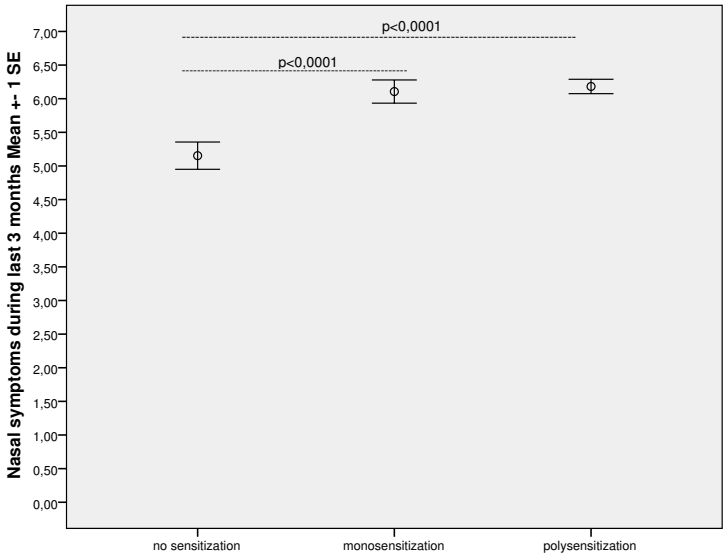

Figure 7.2A:
Perceived severity of nasal symptoms during last 3 months mean SE in non-sensitized, mono- and polysensitized children

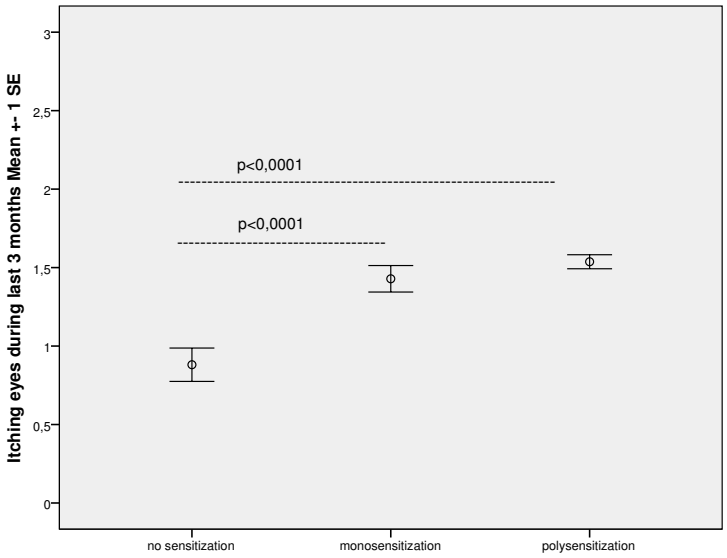

Figure 7.2B:
Perceived severity of eye symptoms during last 3 months mean SE in non-sensitized, mono- and polysensitized children

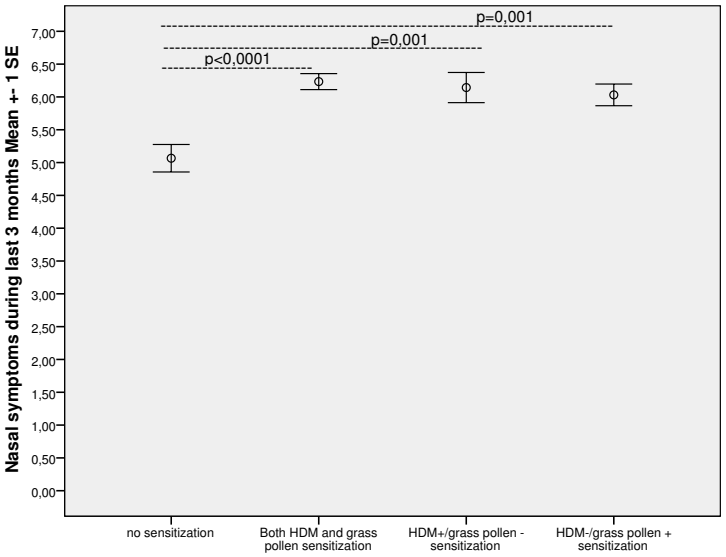

Figure 7.2C:
Perceived severity of nasal symptoms during last 3 months mean SE in non-sensitized, children with both HDM sensitization and grass pollen sensitization, children with a HDM sensitization (without a grass pollen sensitization) and children with a grass pollen sensitization (without a HDM sensitization)

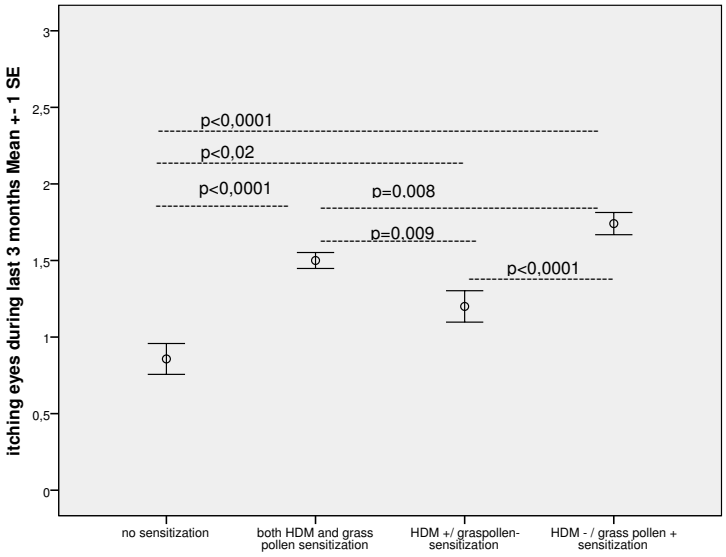

Figure 7.2D:
Perceived severity of eye symptoms during last 3 months mean SE in non-sensitized, children with both HDM sensitization and grass pollen sensitization, children with a HDM sensitization (without a grass pollen sensitization) and children with a grass pollen sensitization (without a HDM sensitization)

three months in children with a HDM sensitization (without a grass pollen sensitization) or a grass pollen sensitization (without a HDM sensitization) or both was significant higher ($p = 0.02$ and $p<0.0001$).

Discussion

This study shows that polysensitization is frequent in children with allergic rhinitis in primary care. Clinical symptoms are equally severe in polysensitized children as in monosensitized children, and are less severe in non-sensitized children. Children with a grass pollen sensitization (without a HDM sensitization) experienced significant higher eye symptoms during the last 3 months compared to children with a HDM sensitization (without a grass pollen sensitization) or both.

Polysensitization is a frequent phenomenon in subjects with allergic rhinitis. This finding is not new, as it was reported in previous studies.[5,8,17] However, these studies were performed in patients in a secondary care setting. In the present primary care study, we found similar results in children diagnosed with allergic rhinitis. About 3/4 of patients were sensitized to two or more allergens. Hence, also primary care physicians should be aware of the fact that patients can have multiple allergies.

The basis of diagnosing allergy consists of a good history and physical examination. However, the diagnosis cannot be confirmed on the basis of symptoms alone, because both allergic and non-allergic conditions can present with similar symptoms.[11] Knowledge of the type of sensitization may affect general practitioners or other physicians in the way they manage children with allergic rhinitis. For example, in the selection of aeroallergens for allergen immunotherapy.[11,18] In our study, 11% of the children were not sensitized. These children were probably either included for relevant medication use or the rhinitis symptoms where misdiagnosed by their physician. In this latter group, symptoms might have been caused by non-immunological aspecific triggers (hyperreactivity). Patients with severe, persisting or recurrent rhinitis symptoms should therefore be tested for specific allergy. 10 The confirmation that an allergen trigger is not the cause may prevent unnecessary lifestyle changes and discourage further allergy investigations.[10,11,18]

A study in a pediatric population showed that children with polysensitization had higher symptom scores and a poorer response to immunotherapy than monosensitized children. Polysensitization seems to be characterized by more severe clinical outcomes compared to monosensitization.[6,17] However, in our study, we found no difference in mean nasal and eye symptom scores in children with different sensitization patterns. Similar results in adults were observed in a study of Malling and collegues.[19] Though, if we compared HDM monosensitization and grass pollen monosensitization, significant difference in eye symptoms were found. A grass pollen induced allergic rhinitis is characterized with more eye symptoms than house dust mite induced allergic rhinitis.[1,2]

In previous studies, the risk of polysensitization was shown to increase with age.[8,20,21] For example Fasce et al. concluded that the number of sensitizations increased with age and monosensitized children are likely to become polysensitized.[20] In our study we saw that increasing age is responsible for an increased expression of polysensitization,

only in the early adolescents. The causes of these age differences may be related to changes in the hormonal environment, environmental factors and behavioral factors (e.g. less frequent outdoor exposure during childhood).[22,23] We can assume there is a link between these factors, but the underlying pathophysiology is unclear.

It is known that in childhood, allergic rhinitis is more common in boys than in girls.[24,25] In our study, we saw no difference in mono- and polysensitization between boys and girls. This is in contradiction with other studies where boys were more likely to be polysensitized than girls.[6,8]

Strengths and weaknesses

This study, conducted in a large group of children with allergic rhinitis in primary care, gives insight in the different patterns of sensitizations and confirms that polysensitization is common in primary care. In The Netherlands, the majority of patients with allergic rhinitis are treated by primary care physicians. Recent articles address the importance of primary care in the treatment and management of allergic rhinitis.[9,26] For these reasons, we considered it important to perform this analysis in a population that was seen in primary care. Future studies designed exclusively to explore the clinical relevance of different (co)sensitization patterns in children should be encouraged.

Both selection bias and reporting bias may have affected our results. The studied population was screened for two randomized double-blind placebo-controlled studies, comparing the efficacy of sublingual immunotherapy with either grass pollen allergen or house dust mite allergen to placebo. This potentially could introduce a bias with regard to the differences between clinical trial participants (i.e. willing to participate in a trial, more severe complaints) and the general population. Also, before inclusion a selection bias could have been introduced. Patients with symptoms due to other allergens than house dust mite or grass pollen most likely did not apply for both studies. These patients could have a mono-sensitization. However, it is also possible that these patients are sensitized to multiple allergens, but mainly affected by an allergen that was not relevant for both studies.

We recognize that selection bias could have affected the results regarding the standard set of allergens that were tested, i.e. grass pollen, HDM, birch pollen and cat dander. Allergen specific IgE to other pet(s) were only determined, if the pet was present at home. Children could thus be sensitized to for example dog dander, but not tested if no dog was present at home. These patients are then incorrectly labeled as monosensitized, indicating that the true number of monosensitized children is even lower than what we found.

Because the nasal and eye symptoms were assessed through interviews, misclassification bias is a concern. Both nasal and eye self-reported symptoms could be underestimated, because of the different seasons when asking the symptoms.

In conclusion, sensitization to multiple allergens occurs frequently in children with allergic rhinitis in general practice. Overall, clinical symptoms are equally severe in polysensitized children as in monosensitized children. Treatment decisions including allergen avoidance measures for allergic rhinitis should be made on the basis of a clinical history and allergy testing.

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Chapter 8

General discussion

Allergic rhinitis (AR) is an inflammatory disease of the nasal membrane and is characterized by symptoms as sneezing, nasal congestion, nasal itching, and rhinorrhea. It is a common condition, affecting approximately 20% of the population.[1] Although allergic rhinitis is not a life-threatening condition, the condition can significantly impair quality of life, despite treatment with antihistamines and nasal corticosteroids. This can lead to a number of direct costs, arising from physician visits, pharmacotherapy costs, as well as indirect costs related to missed days at work or school and a general loss of productivity.[2] Allergen injection immunotherapy significantly reduces symptoms and medication requirements in allergic rhinitis but the use is limited by the possibility of severe systemic reactions.[3] There has been considerable interest in alternative routes for delivery of allergen immunotherapy. Sublingual immunotherapy has the potential to become a useful treatment of allergic rhinitis, because of its convenient form of administration and a good safety profile which allows home administration.[3]

The overall aim of this thesis was to assess the effectiveness of sublingual immunotherapy with house dust mite allergen in children and adolescents, aged 6-18 years in general practice. This chapter summarizes the findings from all chapters of this thesis and discusses the results in a broader context, the strengths and limitations of the study and provides suggestions for future studies.

PREVALENCE OF ALLERGIC RHINITIS

The perception is that the prevalence of asthma and other allergic conditions, such as allergic rhinitis and eczema, are increasing worldwide in the past decades.[4] However, there are conflicting views on time trends of allergic rhinitis during the last 10–15 years. It may be plateauing or even decreasing in areas with a high prevalence.[5]

As discussed in chapter 2, the results in the Netherlands showed an increased incidence in the past decades of allergic rhinitis in children in Dutch general practice. The incidence rate of allergic rhinitis increased from 6.6 (1987) to 9.2 (2001) per 1000 person-years.More recent data showed a significant increase from 21% to 30% in the prevalence of allergic sensitization in children 7 to 8 years old in northern Sweden from 1996 to 2006.[6] In Maltese children (5-8 years), an increasing prevalence of diagnosed asthma (7.5% vs. 14.8%), allergic rhinitis (14.8% vs. 22.2%) and eczema (4.4% vs.11.2%) was seen between 1994-1995 and 2001-2002.[7] On the other hand, in Malta, a significant decrease in the prevalence and improved control of allergic conditions in 13-to 15-yr-old children was seen in the same period (allergic rhinitis(52.7% vs. 50.4%) and eczema (12.8% vs. 11.2%).[5]

Environmental factors have been hypothesized to contribute to the increasing asthma and allergic rhinitis rates including both indoor [8] and air pollution [9], reduced exposure to microbial stimulation, the so called "hygiene hypothesis".[10,11]

A possible explanation of a decrease in prevalence in the last decades could be caused by an increased awareness of asthma and allergic rhinitis among the general public as well as physicians.[12] The increased use of medication may have led to better control of allergic rhinitis and a decreased health care usage by patients. The decrease in doctor diagnosed allergic rhinitis may also be explained by more easily available treatment, antihistaminic tablets (over the counter medication), for patients with allergic symptoms.[13] Increasing prevalence rates among subjects born in the fifties, suggesting a cohort effect, are reported by others as possible factors which could be responsible for the increasing prevalence.[14,15] Changes in lifestyle or environmental factors that occurred around or after 1960 may have contributed to this increase.[15] However, exposure to environmental factors would no longer influence the time trend of asthma and allergies in cohorts born in the eighties.[16] It is doubtful that the stabilizing trend is completely caused by a "stabilization of environment factors". It appears more likely that "saturation" is being reached, i.e. the maximum proportion of the population that has the potential of acquiring asthma and/or getting sensitized may be reached, or in other words that the maximum effect of changing environmental exposure in susceptible individuals may be seen.[17]

Our study showed an increased incidence in the past decades of allergic rhinitis in children in Dutch general practice. Data were used of the first and second Dutch National surveys of general practice, which were performed by the Netherlands Institute for Health Services Research (NIVEL) in 1987 and 2001.[18,19]

For future research, to evaluate the prevalence rates and management of allergic rhinitis in children in the Netherlands (as seen in chapter 2) in more recent years (after 2001), the LINH survey (the Netherlands Information Network of General Practice) could be useful. The LINH survey is a comprehensive longitudinal study allowing to study trends.[20] If a third Dutch National survey could be conducted in the next years, it would be interesting to know, how trends are developing regarding the prevalence and incidence of allergic rhinitis and the management of allergic rhinitis in primary care in the Netherlands. These findings could show, for example, whether treatment of allergic rhinitis by general practitioners is in accordance with the current and revised (2006) clinical guideline of the Dutch College of General Practitioners ('Allergic and non-allergic rhinitis').[21]

QUALITY OF SYSTEMATIC REVIEWS AND META-ANALYSES OF SUBLINGUAL IMMUNOTHERAPY IN CHILDREN

Randomized double-blind placebo-controlled trials, meta-analyses and systematic reviews concerning sublingual immunotherapy have accumulated rapidly in the last years.[22,23] As the findings of chapter 3 indicated, we found few high quality reviews and meta-analysis. In contrast with the increased number of sublingual immunotherapy studies published after 2005 showing better quality of reporting and performing, the methodological quality of the systematic reviews and meta-analysis remains limited and could still be improved.

The included studies in most systematic reviews and meta-analyses on the topic sublingual immunotherapy showed both clinical and methodological heterogeneity, including diverse sources and types of allergen extracts, treatment durations, doses, outcome measures, symptom and outcome scores, rhinitis and/or asthma of different severities, and population (adults vs. children).[24,25] The last decade, the importance has been acknowledged to have explicit and transparent methods to formulate clinically relevant questions, selecting the most relevant outcomes, and searching, appraising and synthesizing the medical literature and performing and reporting a trial. Systematic reviews and/or meta-analysis are regarded as the golden standard.[26] Within the field of immunotherapy, the last couple of years, the essential for proper evaluation and reporting of interventions became well-defined. This resulted in specific guidelines and an adapted CONSORT checklist (Standards of Reporting Trials statement) for trials with allergen-specific immunotherapy.[27-29]

Since 2009, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach is developed to grade the quality of evidence and the strength of recommendations in clinical practice guidelines and its application in the field of allergy. The main advantages of this approach are the focus on the systematic approach to collect the evidence, the clear separation of the concepts of quality of evidence and strength of recommendations, and transparent reporting of the decision process. The focus on transparency facilitates understanding and implementation and should empower patients, clinicians and other health care professionals to make informed choices.[30-32]

In order to promote complete and transparent reporting of randomized controlled trials, systematic reviews and meta-analysis, future studies must comply with guidelines as described. This should stimulate the launch of more valid and adequately designed sublingual immunotherapy trials, in order to assess the appropriate placement of this therapy to treat patients with allergic rhinitis and other allergic diseases, eventually resulting in even more evidence-based guidelines.

SUBLINGUAL IMMUNOTHERAPY EFFECTIVE?

Between 1990 and 2012 more than 105 trials with non-injection routes mostly with grass pollen extracts in children were published. (PubMed search 2012) If we summarize the effectiveness of sublingual immunotherapy with grass pollen allergens, the results are very positive, especially in studies performed in the last four years. These clinical trials determining the efficacy of sublingual immunotherapy involving children have almost exclusively been performed in referral centers.[33,34] Only one study with sublingual immunotherapy in children with a concerned grass pollen-related rhinoconjunctivitis recruited in a primary care setting has been performed.[35] Concerning the positive effectiveness of sublingual immunotherapy, this has become available by testing grass pollen tablet mixtures. Important aspects as dose dependency and efficacy have been partially clarified.[36] High-dose sublingual immunotherapy has been demonstrated to be a safe and effective therapy option for adults and children with grass pollen induced allergic rhinitis.[23,36]

In chapter 5 the results are presented of a randomized placebo controlled trial assessing the effectiveness of sublingual immunotherapy with house dust mite allergen in children in primary care. In our study, sublingual immunotherapy with house dust mite allergen was not better than placebo in reducing rhinitis symptoms in house dust mite-allergic children in primary care. As far as the efficacy of this treatment in children is concerned, evidence for the efficacy of sublingual immunotherapy in children with house dust mite-induced allergy remains inconclusive. Wilson et al concluded there were insufficient data from patients and analysis gave contrasting results for the efficacy of sublingual immunotherapy with house duste mite allergen.[37] Other reviews either suggest promising results or have negative conclusions.[38,39] A meta-analysis of 9 controlled studies on sublingual immunotherapy in mite-induced asthma showed a significant reduction of symptoms ($p = 0.02$) and rescue medication ($p= 0.04$), but the overall number of patients from these nine studies was relatively small (243 verum and 209 placebo) and a relevant inter-study heterogeneity was seen. Despite these limitations, the authors stated that there is promising evidence of efficacy for sublingual immunotherapy with house dust mite extract.[40]

Our study, but also other studies focusing on the effectiveness of sublingual immunotherapy with house dust mite allergen [47,48], clearly shows no robust evidence of efficacy as seen in the latest grass pollen trials. Therefore, treatment of house dust mite induced allergic rhinitis in children with sublingual immunotherapy with house dust mite allergen should not be encouraged as a treatment option for allergic rhinitis.

Primary care population

In our trial, we have chosen to test sublingual immunotherapy with house dust mite allergen in children in primary care as described in chapter 5. Most trials with sublingual immunotherapy were performed in a secondary care setting.[41,42] It is known that about 90% of the patients with allergic rhinitis consulting a general practice have moderate to severe complaints.[43] By selecting primary care patients, a point of criticism can be raised. Our population could be 'too mild' with respect to disease severity. Therefore it could be difficult to detect possible treatment effects, as most trials are performed in referral centers where also these patients have moderate/severe rhinitis.[43,44]

However, our study was designed to comply with current guidelines for the design, analysis and reporting of studies assessing the efficacy of immunotherapy (adaptad Consort statement).[27,45,46] It had a baseline assessment, was placebo-controlled, double-blind, randomized, had an adequate sample size, sufficient duration of treatment, but most important: patients were selected according to predefined clinical criteria, and the primary and secondary outcomes were clearly defined.

Furthermore, for years the manufacture of the studied immunotherapy has advertised and promoted their product, targeting the (Dutch) general practitioners. This strategy has resulted in a substantial prescription of the manufacturers product in Dutch primary care underlining the necessity to evaluate this product in a proper way.

Our baseline nose symptom score of 3.2 points (out of 12) seemed to be low. However, our patients' symptom scores at baseline were even higher, compared to other studies that presented baseline scores. Eifan and colleagues reported a total rhinitis symptom score in three groups at baseline.[41] Patients recorded for a daily evaluation of symptoms according to a four-point scoring system: 0 (no symptoms) to 3 (severe symptoms) for each rhinitis symptoms (sneezing, nasal discharge, itching and nasal obstruction). The total score of all four rhinitis symptoms were termed as total rhinitis symptom scores (TRSS max.12 points) These scores were at baseline for the pharmacotherapy group(n=16) 1.56 ± 1.05, SCIT group(n=16) 1.8 ±0.9 en sublingual immunotherapy group(n=16) 1.3 ±0.9. [41] Also, in the study of Pham-Thi, baseline scores for rhinitis symptoms were very low.[47] Rhinitis symptoms (sneezing, rhinorrhea, nasal blockade, and nasal itching) were recorded as a global score on a diary card at baseline. This global score was rated on a four-point scale, with 0, no symptoms; 1, one or several rhinitis symptoms are present but not disturbing; 2, one or several rhinitis symptoms are present and disturbing; and 3; one or several rhinitis symptoms are present and severe. The verum group (n=54) reported at baseline a rhinitis daily score of 0.71± 0.75 and the placebo group (n=55) a rhinitis daily score of 0.50± 0.58. [47] Hirsh et al. reported a baseline nose symptom score in the verum group (n= 8) of 1.4 (0.25±3.4) and 0.84 (0-3.9) in the placebo group (n=10). The nose symptom score was rated for sneezing, secretion, nasal blockage with 0-3 points.[48] The comparison with the baseline symptoms scores of other studies shows

that the disease severity of our study population, recruited in primary care, cannot be considered to be too mild.

Standardization of allergens

Many reviews have highlighted the difficulty of quantifying the administered dose in terms of micrograms of major allergen, and standardizing this information across a range of studies utilizing allergen extracts from different sources.[22,23]

In Europe, potency determination is based on comparison with in-house (manufacturer-specific) reference standards.[49] Allergen extracts for sublingual immunotherapy are produced by several manufacturers, with administration schedules and amount of allergen(s) that vary considerable between products.[50]

In our randomized trial (chapter 5), the total dose was 435 micrograms equivalent *Der p1* given over 24 months. The cumulative dose in our study seemed relatively low compared to most other studies.[40] If we compare sublingual immunotherapy with house dust mite allergen studies in children with a diagnosis of allergic rhinitis (and/or asthma), different cumulative doses are reported (Table 8.1).[40] Hirsh et al. reported a cumulative dose of 570 mcg for a duration of 1 year.[48] The study of Bahçeciler reported a cumulative dose of 560 mcg over 6 months.[51] Pham-Thi performed a study in children with house dust mite-induced allergic asthma for 18 months with a cumulative dose of 6900 mcg Der. p1 and 14700 mcg Der. f1.[47] The latest Cochrane review summarized 49 studies, 32 reported the daily major allergen dose in a manner suitable for meta-analysis. The remaining trials either did not provide sufficient data or only reported the cumulative dose. Only eight trials used daily doses of less than 5mcg, in 12 studies the dose was between 5 and 20 mcg per day, and 12 papers reported a daily dose of more than 20 mcg. of major allergen. [23]

Table 8.1: Reported cumulative doses in house dust mite immunotherapy trials40

Author	Cumulative dose	Duration
Hirsch 1997 48	570 mcg Der p1	12 months
Bousquet 1999 52	104 000 IR, 4200 mcg Der p1	24 months
Pajno 2000 53	360 mcg Der p1	24 months
Bahcecilier 2001 51	7.000 IR, 560 mcg Der p1	6 months
Niu 2006 42	1700 mcg Der p1, 3000 mcg Der f1	6 months
Lue 2006 54	Der f 1.Cumulat. 1700 mcg Der p1	6 months
Pham-Thi 2007 47	155 000 IR, 6900 mcg Der p1, 14700 mcg Der f1	18 months
De Bot 2012	435 mcg Der p 1	24 months

STU, Specific treatment units; IR, Index of reactivity; AU, Allergic units; BU, Biologic units

A wide variety of allergen preparations and a lack of information concerning the dose expressed in micrograms of major allergen and the biological activity of the allergen preparations make it difficult to compare studies. The characteristics of individual SLIT products might also contribute to the differences in clinical outcomes of the SLIT trials.[55] There is still debate on what the optimal dosage and duration of treatment should be. This information is essential, when comparing studies regarding the optimal dose, duration and the biological activity of the allergen product, and to solve dose-response aspects. It would also provide a support for investigating the mechanisms.[56] The limited generalizability of efficacy of sublingual immunotherapy showed clearly the limitations of systematic reviews and meta-analyses, when including products with very heterogeneous single and cumulative doses.[57] Therefore, it would be essential to do additional analyses of efficacy of sublingual immunotherapy on a product-specific basis without generalizing to the whole class of allergens.[58] The distinction should be made between different products until comparability of preparations can be demonstrated.[58]

MONOSENSITIZATION VERSUS POLYSENSITIZATION

It has been suggested by the ARIA group that patients with multiple sensitivities may not benefit from specific immunotherapy as much as patients with a single sensitivity.[3] However, polysensitization is quite frequent in allergic children and may cause difficulties for the physician when prescribing allergen-specific immunotherapy.[2,3]

In chapter 4 and chapter 7 we showed that more than 80% of the children in our study were polysensitized, 22% were even sensitized to 4 aeroallergens. The use of sublingual immunotherapy in polysensitized patients is still a matter of debate. The last five years several clinical trials have been designed to dissect the response of sublingual immunotherapy in patients with single versus multiple sensitizations.[59,60] In a study of Malling et al. studying the efficacy and safety of five different grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitic, the efficacy of 5-grass pollen sublingual immunotherapy tablets was observed in patients who were polysensitized in contrast to patients who were allergic only to grass pollen (monosensitized).[33]

The World Allergy Organization (WAO) Position Paper (2009) suggested for trials to evaluate the clinical efficacy of sublingual immunotherapy to include only monosensitized patients.[45] Thus, performing a study with only monosensitized children would be ideal according to these guidelines. This selection of patients would be homogeneous for disease severity and results would not be confounded by symptoms of competing allergens.[45] Nevertheless, for practical reasons such as time consumption for including only mono-sensitized subjects, budget and limited number of mono-sensitized subjects

[45], Ciprandri et al. concludend that polysensitization should not be an obstacle for including children in sublingual immunotherapy trials.[60]

But more important: the clinical relevance of a trial with only monosensitized patients is doubtful, as the majority of patients with allergy are polysensitized. The choice of using sublingual immunotherapy in polysensitized subject should be limited to one or two allergen extracts, preferably separated and at high dosages.[61] The latest review about multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients concluded that single-allergen immunotherapy with grass pollen extract has proved to be as safe and effective in polysensitized patients. However, sublingual or subcutaneous multiallergen immunotherapy in polysensitized patients needs more supporting data from large clinical trials to validate it as a treatment option.[63]

Chapter 7 showed also that clinical symptoms of allergic rhinitis were equally severe in polysensitized children as in monosensitized children. Therefore, the basis of a diagnosis of allergy requires a good history and examination. However, the diagnosis cannot be confirmed on the basis of symptoms alone, because both allergic and non-allergic conditions can present with similar symptoms.[63] Treatment decisions for allergic rhinitis should be made on the basis of a clinical history and after confirmation through allergy testing. The confirmation that an allergen trigger is not the cause for clinical symptoms may prevent unnecessary lifestyle changes and discourage further allergy investigations.[63,64]

In general practice, the medical history, related to timing of the symptoms, trigger factors, and evidence of personal and family history of allergic disease, should guide the need for, and choice of a diagnostic allergy test. The need for a allergy test should therefore depend on whether or not the identification of an allergen trigger will influence the treatment decision.[65] For example if an allergen-specific treatment such as immunotherapy is being considered, then identification of the specific allergen trigger is essential.

ADHERENCE

In treating allergic diseases, dealing with non-compliance is essential given its association with failure to achieve the desired effect of treatment and prevention of more medical cost.[66] The latter is particularly important, because sublingual immunotherapy is self-administrated at home over a period of several years, as this time is supposed to be required to achieve the immunological changes needed to ensure the clinical effects of sublingual immunotherapy. This makes compliance issues even more relevant.[3]

In our trial, described in chapter 5, the proportion of patients taking ≥ 80% of the calculated dose was 81% in the placebo group and 86% in the active group (p= 0.38).

Thus, our trial with a duration of 2 years demonstrated an overall high adherence rate. Only a few papers about the topic "compliance" or "adherence" with sublingual immunotherapy in children have been published.[67,68] A study with a duration comparable to ours found an average adherence rate of 77% in 154 children and investigated also factors (for example age, disease severity, medication instructions) that may influence adherence to sublingual immunotherapy. Drop-out was affected by age, evaluation of the treatment effect and medication instructions.[67] Pajno and colleagues reported in an observational study, the drop-out rate and the reasons for stopping immunotherapy in children (6-15 years) using subcutaneous immunotherapy, sublingual immunotherapy or local nasal immunotherapy.[68] The drop-out rates after 3 years were 11%, 21.5% and 73% for subcutaneous immunotherapy, sublingual immunotherapy and local nasal immunotherapy, respectively. A significant better compliance rate was registered in a hospital setting (90.5%), in comparison with a private practice (61.2%).[68]

Niu et al reported on the number of patients who discontinued treatment and its reasons in a multi-center, double-blind, randomized, and placebo-controlled study on the efficacy of sublingual immunotherapy with high-dose mite extracts in asthma.[42] Thirteen patients, seven from verum group and six from placebo group, withdrew or terminated early from the study due to lack of direct efficacy, loss to follow-up or withdrawn consent.[42] Concerning perceived efficacy, it was observed that a lack of compliance to SLIT may be caused by the erroneous perception that once allergic symptoms are improved, SLIT is no longer needed.[69] In a survey on the allergist's opinion about the factors positively influencing the adherence to SLIT, the issues judged most important were the patient's perception of efficacy, reimbursability, tolerability, and the patient's education.[70]

The adherence rate in our study was high compared to studies with a comparable study duration. It is, however, difficult to compare some of these data to our study as our participants were more frequently supervised for a longer period of time and because different definitions of adherence are used. The adherence to treatment in daily clinical practice will be lower than in a clinical trial, due to the attention participants receive during participation in a clinical trial and the selection of patients that are willing to participate in a study. However, adherence data in a clinical trial are essential for the interpretation of the clinical effect of sublingual immunotherapy, as adherence is regarded as one of the major determinants of a successful treatment.

Thus, patient education and regular control visits are crucial issues for adherence. Ideally, when a patient starts with SLIT, patients should receive an educational course on SLIT en regular control visits would improve the adherence to immunotherapy.

FRACTION INHALED NITRIC OXIDE

Recent studies on FeNO have shown elevated levels in for example children with asthma, allergic rhinitis or atopic eczema.[71,72] Most of these studies have been conducted in children without measuring respiratory symptoms. In our study as presented in chapter 6, FeNO was not associated with reported upper airway complaints in this primary care population of children with allergic rhinitis. A weak correlation was found between FeNO level and asthma symptoms. Previous studies have shown a relationship between exhaled NO and mainly asthma symptoms. At best, these correlations are also weak to moderate.[73,74] FeNO levels in patients with rhinitis suggest the presence of inflammation in the lungs, even in the absence of asthma symptoms.[75] High FeNO levels in an asthmatic child could not only be caused by a poor control of asthma, but also by the persistence of rhinitis symptoms in the asthmatic child. It is however, unknown to what extent the therapeutic management of allergic rhinitis may impact asthma control in the child or the other way around.[76]

Within the concept that upper and lower airways have a close link, the question still remains whether atopy rather than asthma or both would explain elevated FeNO levels. Recent studies on FeNO have shown increased levels in non-asthmatic patients with other atopy related diseases such as allergic rhinitis.[77,78] The increase of FeNO in non-asthmatic individuals suggests that FeNO reflects allergic inflammatory activity of the airways, depending on the degree of atopy.[79] In our study, we did not find differences in FeNO levels between children with allergic rhinitis or children with allergic rhinitis and asthma, similar as seen in the study of Chawes, indicating that both children with allergic rhinitis and asthma and children with allergic rhinitis only have raised levels of FeNO.[80]

According to the latest guidelines on the treatment and control of allergic rhinitis, systematic evaluation of airway inflammation in patients with allergic rhinitis and asthma should be encouraged, recognizing the importance of the concept of 'one airway disease'.[3,76]

In primary care, FeNO measurement can be clinically useful in the diagnosis and monitoring of asthma, not specific for allergic rhinitis. However, due to phenotypic distinctions and variability in the underlying pathology of asthma and other respiratory conditions, FENO should not be the sole determinant of an asthma diagnosis.

IMPLICATIONS FOR PRACTICE

For children with house dust mite induced allergic rhinitis, more evidence is needed on the efficacy of sublingual immunotherapy with house dust mite allergen, as some well

conducted trials and systematic reviews show inconclusive results.[22,23,38,40] Nevertheless, treatment with sublingual immunotherapy in children with grass pollen induced allergic rhinitis could be of considerable interest. This therapeutic approach has proven to be effective and safe for the treatment of allergic rhinitis the last two years.[23,33,34] The efficacy of sublingual immunotherapy with house dust mite allergen in children remains an unanswered question. At least, the HDM-SLIT product, studied in this trial, with a relatively low dosage, was not effective in this primary care population of children with allergic rhinitis. Our study was designed to comply with current guidelines for the design, analysis and reporting of studies assessing the efficacy of immunotherapy. The latest update of the Cochrane review on efficacy of sublingual immunotherapy advises to interpret these findings with caution.[23] The majority of the included trials were small and the heterogeneity in this group was high. Ongoing and future clinical trials of, for example, standardized tablet products with house dust mite allergen may reveal the answers within a few years.

Recent guidelines address the importance of the role of primary care in the treatment and management of allergic rhinitis.[81] The World Allergy Organization proposed more collaboration between primary care and allergologists for an optimal delivery of sublingual immunotherapy in the community setting.[45] For now, in Dutch general practice, this is a bridge too far. The Dutch guideline 'Allergic and non-allergic rhinitis' still state that treatment of allergic rhinitis with immunotherapy in primary care is limited.[21]

As there is more data available for the efficacy of sublingual immunotherapy, especially for grass pollen induced allergic rhinitis with registered products, the next question to be answered is: if a patient asks for these products, what should a general practitioner decide to prescribe? The basis for this decision-making process should be the consideration that the choice to treat children with sublingual immunotherapy has to be product-based by assessing the available level of scientific information for the respective allergen products for example GRAZAX®.[21,58]

IMPLICATIONS FOR FUTURE STUDIES

Our trial was the first to assess the effect of sublingual immunotherapy with house dust mite allergen in children with allergic rhinitis in primary care. Several questions need to be answered before sublingual immunotherapy with house dust mite allergen can be used outside of the research domain. Future studies should be randomized placebo-controlled dose-finding studies to determine the optimal and safe dose and duration. More attention should be paid to well designed randomized double-blind placebo-controlled trials, improvement of quality of life of allergic children and the adherence aspect of sublingual immunotherapy. More detailed and proactive documentation of

side effects is required. Intervention studies can provide evidence for cost- effective treatment for a large group of children who are presenting their complaints of allergic rhinitis.

In conclusion, allergic rhinitis is a common chronic disorder in children and is frequently presented in Dutch primary care. Sublingual immunotherapy has the potential to become an useful treatment of allergic rhinitis, which can can alter the course of allergic rhinitis, has a convenient form of administration and a good safety profile which allows home administration. New findings from ongoing and future research will hopefully contribute to assess the appropriate place for sublingual immunotherapy with house dust mite allergen in the treatment of patients with allergic rhinitis in Dutch primary care.

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Summary

Allergic rhinitis is a highly prevalent chronic disease in children and adults which can affect quality of life despite optimal treatment. During the decade the prevalence of allergic rhinitis has increased. Therapeutic options are allergen avoidance, medical interventions and allergen-specific immunotherapy. Sublingual immunotherapy is a method of allergy treatment that uses an allergen solution given under the tongue, with the aim to reduce sensitivity to allergens. Sublingual allergen immunotherapy (SLIT) has been demonstrated to be safe and could be effective in the treatment of allergic respiratory diseases in children. Numerous studies and reviews on the efficacy of sublingual immunotherapy showed contradictive results. The main objective of this thesis are the results of a randomized double blind placebo-controlled trial, studying the efficacy of sublingual immunotherapy with house dust mite allergen (SLIT-HDM) in 6 to 18-year-old children with allergic rhinitis and a proven house dust mite allergy in primary care.

In **chapter 2** we compared incidence rates and management of allergic rhinitis presented by children aged 0-17 years in general practice between 1987 and 2001. The incidence rate of allergic rhinitis increased from 6.6 (1987) to 9.2 (2001) per 1000 person-years. We found a male predominance with a switch in adolescence to a female predominance at both time points. Compared to 1987, in 2001, the incidence rate of allergic rhinitis had increased significantly in rural areas (<30,000 inhabitants) from 5.1 to 9.0 and suburban areas (30,000 – 50,000 inhabitants) from 7.0 to 9.9, ($p<0.001$ and $p=0.019$, respectively). In 2001, children of natives and western immigrants visited the general practitioner more often with complaints of allergic rhinitis compared to 1987. In both surveys the majority of children were treated with decongestants or other nasal preparations and antihistamines, which is in accordance with the 1996 clinical guideline. From 1987 to 2001 the prescriptions for antihistamines rose from 23% to 45%. The proportion of prescriptions for drugs for nasal symptoms remained stable over the last 15 years, whereas prescriptions for anti-inflammatory eye drops increased from 7% to 13%. The prescriptions in 1987 showed a wider variety of medication type shifting in 2001 to a smaller spectrum. The shift to a smaller spectrum of prescriptions in 2001 may be a result of the 1996 clinical guideline.

Systematic reviews have gained popularity as a way to combine the increasing amount of research information. Several reviews and meta-analyses have been published regarding the efficacy of sublingual immunotherapy in children. **Chapter 3** describes the assessment of the quality of available systematic reviews and meta- analyses of sublingual immunotherapy for allergic rhinitis in children published since 2000. The AMSTAR measurement tool was used to assess the methodological quality of systematic reviews. Eligible reviews were identified by searching Medline, Embase and the Cochrane Library, from 2000 through 2008. Ten systematic reviews were included, one of which

was published in the Cochrane Library. Eight reviews gave some details about the search strategy. None of the reviews included measures to avoid selection bias. In six reviews the methodological quality of the included studies was (partly) assessed. Four reviews pooled results of individual studies, neglecting clinical heterogeneity. Three of the 10 reviews provided information about sources of funding, or grants from industry. Of the 10 reviews, the 6 reviews with the highest overall score scored 5-8 points out of a maximum of 11. indicating moderate quality. Systematic reviews are useful to evaluate the efficacy of sublingual immunotherapy in children. Although more reviews have become available, the methodological quality could be improved. Sublingual immunotherapy for children could be promising, but methodological flaws in the reviews and individual studies are too serious to draw definite conclusions. A systematic review is a useful tool for evaluating the efficacy of sublingual immunotherapy in children. Consensus agreement and further guidance is needed to enhance the quality of the systematic reviews in this area.

Chapter 4 describes the detailed study design of the trial that we preformed to test the effectiveness of sublingual immunotherapy with house dust mite allergen in 6 to 18-year-old children with allergic rhinitis and a proven house dust mite allergy in primary care. The recruitment strategy and main characteristics of the children are presented. A total of 226 general practitioners invited almost 6000 children. The target sample size was 256 children; 251 patients were finally included, meaning 98% of the target sample size was achieved. The most frequently mentioned reasons for not participating were: absence or mildness of symptoms and being allergic to grass pollen or tree pollen only. Asthma symptoms were reported by 37% of the children. Of the enrolled children, 71% was sensitized to both house dust mite and grass pollen. Roughly similar proportions of children were diagnosed as being sensitized to one, two, three or four common inhalant allergens. This study was designed in accordance with recent recommendations for research on establishing the efficacy of sublingual immunotherapy.

Chapter 5 gives insight in the results of the randomized controlled trial (RCT). Children were randomly allocated to either sublingual immunotherapy with house dust mite allergen or placebo for the duration of two years. The primary outcome was the efficacy of sublingual immunotherapy with house dust mite allergen compared to placebo. Primary outcome parameter was the mean total nose symptom score (rhinorrhea, blocked nose, sneezing, itching; scale 0-12) during the autumn of the second treatment year. Secondary outcome measures were for example the proportion of symptom-free days, rhinitis specific quality of life and compliance. Baseline demographic and clinical variables were similar in the 251 included children. Overall, the mean nose symptom score ± SD after 2 years of treatment did not show a significant effect of sublingual immunotherapy (symptom score 2.26 ± 1.84 versus placebo, 2.02 ± 1.67, p=0.08). There were no significant differences regarding secondary outcomes (medication scores,

symptom free days) or in subgroup analysis. Rhinitis specific Quality of life did not differ between the active study drug group group and the placebo group. The proportion of patients taking ≥ 80% of the calculated dose was 81% in the placebo group and 86% in the active group (p= 0.38). The subgroup analyses of the severity of nasal symptoms at baseline(nasal symptom score at baseline <3 and ≥ 3), the severity of the dust mite specific IgE test (HDM CAP-class 2 and ≥ 3) and having only house dust mite allergy (monosensitization) or dust mite allergy and other allergies (polysensitization) also showed no difference between the two treatment groups. The total cumulative dose in a fully compliant patient over the 2-year period was estimated at 435 mcg *Der p1*. The number of patients reporting adverse events was comparable between both groups. No systemic anaphylactic reactions were reported. In conclusion, sublingual immunotherapy with house dust mite allergen with a relatively low dosage was not better than placebo in reducing rhinitis symptoms in house dust mite-allergic children in primary care. Sublingual immunotherapy as administered in this study can be considered safe.

Allergic rhinitis and asthma are both inflammatory diseases and are often associated. Previous studies have shown a relationship between fractional exhaled nitric oxide (FeNO) and asthma, atopy, total and specific IgE and quality of life. **Chapter 6** describes whether FeNO in children with allergic rhinitis or combined allergic rhinitis and asthma was associated with nasal and asthma symptoms, house dust mite-specific (HDM) IgE and rhinitis-specific quality of life, both cross-sectional and longitudinal. We found similarly elevated FeNO in children with only AR (n=158) and combined AR and asthma (n=93). Children with AR only had significant lower scores on the RQLQ, indicating a better rhinitis specific quality of life compared to children with both AR and asthma at baseline. Children with AR and asthma had significant higher levels of house dust mite-specific IgE in both years, compared to children with only AR (p=0.002 and p=0.001).

No correlations were found between FeNO and nasal or asthma symptoms and rhinitis-related quality of life. Longitudinal correlations were strongest for HDM specific IgE (r= 0.911, p < 0.0001). FeNO was similar in children with AR with and without asthma and was unrelated to symptoms or quality of life in both groups. FeNO was related to specific IgE to HDM at baseline and at two years. FeNO is unlikely to be a useful measure of upper or lower airway disease severity in primary care.

Polysensitization is a frequent phenomenon in patients with allergic rhinitis.

Chapter 7 describes the pattern of sensitization to common allergens and the association with age, gender and clinical symptoms in children in primary care who are diagnosed with allergic rhinitis. In a cross-sectional study, children with allergic rhinitis aged 6 to18 years (n=784) in primary care were assessed for age, gender, specific IgE, nasal and eye symptom scores. With regard to the specific IgE, type and number of sensitizations were considered.

In 699/784 children (89%) a positive IgE test for one or more allergens was found. Polysensitization (≥ 2 sensitizations) was found in 69% of all children. Sensitization was more common in children aged 9 to 13 than in younger children (5 - 8 year) (p=0.03). Mono,- and polysensitization was not significantly different in both girls and boys. Severity of clinical symptoms did not differ between polysensitized children and monosensitized children, but the symptoms were significantly lower in non-sensitized children.

Polysensitization to multiple allergens occurs frequently in children with allergic rhinitis in general practice. Overall, clinical symptoms are equally severe in polysensitized children as in monosensitized children. Treatment decisions for allergic rhinitis should be made on the basis of a clinical history and allergy testing.

Chapter 8 summarizes and reflects on the main findings emerging from this thesis. Furthermore, the limitations of the study and implications of the results for general practice and future research are discussed. Future studies should be randomized placebo-controlled dose-finding studies to determine the optimal and safe dose and duration of treatment with sublingual immunotherapy. In these trials, the improvement of quality of life of allergic children and the adherence aspect of sublingual immunotherapy should additionally be focused on. The findings presented in this thesis and new findings from on-going and future research will hopefully contribute to establishing the optimal place of treatment with sublingual immunotherapy of patients with allergic rhinitis in Dutch primary care.

Samenvatting

Allergische rhinitis is een veel voorkomende chronische aandoening bij kinderen en volwassenen die de kwaliteit van leven negatief kan beïnvloeden, ondanks optimale behandeling. Veel voorkomende oorzaken zijn een allergie tegen graspollen of boompollen (hooikoorts), katten of huisstofmijt. De stoffen waar iemand allergisch voor is worden allergenen genoemd. Er zijn verschillende therapeutische mogelijkheden, zoals vermijding van blootstelling aan het allergeen, farmacotherapie en allergeenspecifieke immunotherapie. Sublinguale immunotherapie (SLIT) zou een veilige en doeltreffende behandeling kunnen zijn bij de behandeling van allergische rhinitis bij kinderen. Immunotherapie is een behandelmethode waarbij kleine hoeveelheden van de stof waar een patiënt allergisch voor is (de allergene stof), toegediend worden. Dit gebeurt door deze allergene stof als druppels of tablet onder de tong (sublinguaal) te brengen. Verschillende reviews en meta-analyses zijn gepubliceerd over de effectiviteit van sublinguale immunotherapie bij kinderen. De conclusies over de werkzaamheid van sublinguale immunotherapie zijn tegenstrijdig. Dit proefschrift beschrijft de opzet en de resultaten van een gerandomiseerd dubbelblind placebo-gecontroleerde trial, waarbij het effect wordt onderzocht van sublinguale immunotherapie met huisstofmijtallergeen (SLIT-HDM) bij kinderen van 6 tot 18 jaar met allergische rhinitis in de huisartsenpraktijk.

Hoofdstuk 2 vergelijkt de incidentiecijfers en behandeling van allergische rhinitis bij kinderen in de leeftijd van 0-17 jaar in de Nederlandse huisartsenpraktijk in 1987 en in 2001. De incidentie van allergische rhinitis gaat over het aantal nieuwe patiënten met allergische rhinitis in een omschreven populatie tijdens een omschreven periode. De totale incidentie van aan de huisarts gepresenteerde nieuwe klachten van allergische rhinitis steeg van 6,6 per 1000 persoonsjaren in 1987 tot 9,2 in 2001, een statistisch significant verschil. Jongens voor de puberteit komen vaker met klachten van allergische rhinitis bij de huisarts, maar meisjes in de puberteit gaan vaker naar de huisarts met klachten van allergische rhinitis op beide tijdpunten. Vergeleken met 1987 was de incidentie van allergische rhinitis in 2001 in landelijke gebieden (<30.000 inwoners) gestegen van 5,1 naar 9,0 per 1000 persoonsjaren, en in verstedelijkte gebieden (30.000 - 50.000 inwoners) van 7,0 naar 9,9 per 1000 persoonsjaren. In 2001 bezochten de kinderen van autochtone inwoners en de westerse immigranten vaker de huisarts met klachten van allergische rhinitis dan in 1987. In 1987 bestond de voorgeschreven medicatie hoofdzakelijk uit corticosteroïden toegediend via de neus (36%) en in 2001 ging het vooral om orale antihistaminica (45%). Het aandeel recepten voor orale antihistaminica steeg van 23% naar 45%. Het percentage recepten voor geneesmiddelen voor neusklachten is stabiel gebleven in de afgelopen 15 jaar, terwijl het aantal recepten voor anti-inflammatoire oogdruppels gestegen is van 7% tot 13%. De voorschriften in 1987 lieten een grotere verscheidenheid van medicatiesoorten zien dan in 2001. Deze

verschuiving naar een kleiner spectrum van medicatievormen in 2001 kan het resultaat zijn van de publicatie van de richtlijn "Allergische rhinitis" van het Nederlands Huisartsen Genootschap in 1996.

Systematische reviews vormen een efficiënte en betrouwbare informatiebron voor de clinicus, beleidsmaker en onderzoeker. Systematische reviews zijn steeds populairder geworden als een manier om de toenemende hoeveelheid onderzoekspublicaties te combineren. De laatste jaren zijn er veel reviews en meta-analyses gepubliceerd over de effectiviteit van sublinguale immunotherapie als behandelmethode van allergische rhinitis bij kinderen. **Hoofdstuk 3** beschrijft de inventarisatie van de kwaliteit van de beschikbare systematische reviews en meta-analyses van sublinguale immunotherapie voor allergische rhinitis bij kinderen, die gepubliceerd zijn sinds 2000. Het AMSTAR meetinstrument werd gebruikt om de methodologische kwaliteit van systematische reviews te beoordelen. Reviews die mogelijk in aanmerking zouden komen, zijn geïdentificeerd door te zoeken in Medline, Embase en de Cochrane Library, van 2000 tot 2008. Tien systematische reviews werden opgenomen, waarvan er een werd gepubliceerd in de Cochrane Library. Acht reviews rapporteerden details over de zoekstrategie. Geen van de reviews beschreef maatregelen om eventuele selectiebias te voorkomen. In zes reviews werd de methodologische kwaliteit van de geïncludeerde studies (gedeeltelijk) beoordeeld. Vier reviews namen resultaten van de afzonderlijke studies samen, maar hielden geen rekening met klinische heterogeniteit. Drie van de 10 reviews verstrekten informatie over de bronnen van financiering of subsidies. Van de 10 reviews waren er zes, die een totaalscore hadden van 5-8 punten. Het maximum aantal punten was 11 punten. Dit houdt in dat de reviews van matige kwaliteit zijn. Een systematische review is een nuttig hulpmiddel om de effectiviteit van sublinguale immunotherapie bij kinderen te evalueren of voor het interpreteren van de resultaten. In de laatste jaren is het aantal gepubliceerde systematische reviews gestegen, maar de kwaliteit is zeker nog niet optimaal. Sublinguale immunotherapie voor kinderen zou veelbelovend kunnen worden, maar methodologische tekortkomingen in de reviews en meta-analyses en tevens ook in individuele studies zijn te ernstig, om definitieve conclusies te kunnen trekken Eenduidige richtlijnen zijn nodig om de kwaliteit van systematische reviews te verbeteren.

Hoofdstuk 4 beschrijft het gedetailleerde studieprotocol van de trial die we uitvoerden. In dit hoofdstuk komen ook de werving en de belangrijkste baselinekenmerken van de deelnemers aan de orde. Een totaal van 226 huisartsen nodigden bijna 6000 kinderen uit. Het benodigde aantal kinderen voor deze studie was 256; 251 kinderen tussen 6-17 jaar zijn uiteindelijk geïncludeerd, 98% van het vooraf berekende aantal. De gemiddelde leeftijd was 11,8 jaar en 59% was jongen. De meest gerapporteerde redenen om niet deel te nemen aan het onderzoek waren: ontbreken van symptomen of slechts milde klachten, geen huisstofmijtallergie en alleen graspollen- en/of boompol-

lenallergie. Symptomen van astma werden gemeld door 37% van de kinderen. Van de deelnemende kinderen was 71% allergisch voor zowel huisstofmijt als graspollen. De meerderheid van de kinderen was allergisch voor twee of meer allergenen (77%). Deze studie was opgezet volgens de meest recente richtlijnen voor het opzetten en uitvoeren van onderzoek naar de effectiviteit van sublinguale immunotherapie.

Hoofdstuk 5 beschrijft de resultaten van de dubbel- blind placebo- gecontroleerde trial (RCT). De kinderen werden willekeurig toegewezen aan behandeling met sublinguale immunotherapie met huisstofmijtallergeen danwel placebo voor de duur van twee jaar. De primaire uitkomstmaat was de effectiviteit van sublinguale immunotherapie met huisstofmijtallergeen vergeleken met placebo op de neusklachten (niezen, jeukende neus, loopneus, verstopte neus; schaal 0-12) na 2 jaar behandeling. Secundaire uitkomstmaten waren onder andere het percentage dagen zonder klachten, rhinitis specifieke kwaliteit van leven en therapietrouw. Er werden 251 kinderen geïncludeerd. De twee groepen waren bij baseline vergelijkbaar qua demografische en klinische kenmerken. Na 2 jaar behandeling was er geen verschil tussen de groep die huisstofmijtallergeen kreeg en de groep die placebo druppels kreeg (neussymptoomscore 2,26 ± 1,84 bij de groep die huisstofmijt allergeen kreeg en 2,02 ± 1,67,bij de groep die placebo druppels kreeg) p=0,08). Er waren geen significante verschillen in secundaire uitkomsten tussen behandeling met sublinguale immunotherapie met huisstofmijtallergeen en placebo. Rhinitis specifieke kwaliteit van leven verschilde niet tussen de groep die huisstofmijtallergeen kreeg en de groep die placebo druppels kreeg. De subgroepanalyses naar de ernst van de klachten aan het begin van de studie (neussymptoomscore <3 en ≥ 3), de ernst van de huisstofmijt specifiek IgE test (HDM CAP-class 2 en ≥ 3) en het hebben van alleen huisstofmijtallergie (monosensibilisatie) of huisstofmijt allergie en meerdere allergieën (polysensibilisatie) lieten ook geen verschil zien tussen beide behandelgroepen. Kinderen die gedurende de studie 80% of meer van de voorgeschreven medicatie hadden ingenomen werden beschouwd als therapietrouw. In de groep die huisstofmijt allergeen kreeg was 86% therapietrouw en in de groep die placebo druppels kreeg was dat 81% (p=0,38). De gemiddelde totale voorgeschreven dosis van het huisstofmijtallergeen was 435 mcg *Der p1*. Het aantal patiënten dat een bijwerking meldde was ook vergelijkbaar tussen beide groepen. Er werden geen ernstige systemische reacties gemeld. Concluderend kan gezegd worden dat sublinguale immunotherapie met de onderzochte dosering huisstofmijtallergeen geen effect heeft in vergelijking met placebo op het verminderen van rhinitissymptomen bij huisstofmijt allergische kinderen in de eerstelijnsgezondheidszorg. Sublinguale immunotherapie zoals toegediend in deze studie kan als veilig worden beschouwd.

Allergische rhinitis en astma zijn verwante chronische ontstekingsziekten van respectievelijk de onderste en bovenste luchtwegen. Eerdere studies hebben aangetoond dat er een relatie is tussen de hoeveelheid stikstofmonoxide in de uitademingslucht

(FeNO) en astma, atopie, specifiek IgE bloedtest en kwaliteit van leven. In **hoofdstuk 6** gaan we na of FeNO bij kinderen met allergische rhinitis of allergische rhinitis en astma geassocieerd was met neus- en astmasymptomen, huisstofmijt-specifieke IgE bloedtest en rhinitis-specifieke kwaliteit van leven. Dit is zowel cross-sectioneel als longitudinaal onderzocht. Bij cross-sectioneel onderzoek wordt ieder individu eenmaal geobserveerd of gemeten. Bij longitudinaal onderzoek worden de waarnemingen of metingen bij ieder individu op een aantal achtereenvolgende tijdstippen herhaald. FeNO was even hoog bij kinderen met allergische rhinitis (n = 158) als bij kinderen met allergische rhinitis én astma (n = 93). Kinderen met allergische rhinitis hadden lagere scores bij rhinitis-specifieke kwaliteit van leven vragenlijst dan bij kinderen met allergische rhinitis én astma. Dit betekent dat kinderen met alleen allergische rhinitis minder gehinderd worden door hun klachten in de dagelijkse activiteiten en (school) werk dan kinderen met allergische rhinitis én astma. Kinderen met allergische rhinitis én astma hadden hogere huisstofmijt-specifieke IgE waardes op beide meetmomenten in vergelijking met kinderen met uitsluitend allergische rhinitis (p = 0,002 en p = 0,001).

Er werden geen correlaties gevonden tussen FeNO en neus- en astmaklachten en kwaliteit van leven. Een matige correlatie werd gevonden tussen FeNO en huisstofmijt-specifieke IgE aan het begin van de studie (r = 0,404, p <0,0001). Longitudinale correlaties waren het sterkst voor huisstofmijtspecifieke IgE (r = 0.911, p <0,0001). We concluderen dat het meten van FeNO bij kinderen met allergische rhinitis in de huisartsenpraktijk geen toegevoegde waarde heeft voor ons inzicht in de ernst van de klachten.

Het hebben van meerdere allergieën (polysensibilisatie) is een veel voorkomend fenomeen bij patiënten met allergische rhinitis. **Hoofdstuk 7** beschrijft of het hebben van meerdere allergieën geassocieerd is met leeftijd, geslacht en neus- en oogsymptomen bij kinderen uit de huisartsenpraktijk met de diagnose allergische rhinitis. In deze studie zijn 784 kinderen met allergische rhinitis in de leeftijd van 6 tot 18 jaar beoordeeld op leeftijd, geslacht, specifiek IgE, neus- en oogsymptoomscores. Met betrekking tot de specifieke IgE werd gekeken naar welke soorten allergieën er speelden (b.v. graspollen of huisstofmijt) en het aantal allergieën.

Bij 89% van de kinderen werd een positief IgE test gevonden voor een of meer allergenen. Polysensibilisatie (≥ 2 allergieën) werd gevonden bij 77% van alle kinderen. Een sensibilisatie kwam meer voor bij kinderen van 9 tot 13 jaar (66%) dan bij jongere kinderen (5 - 8 jaar) (53%) (p = 0,03). Mono-, en polysensibilisatie was niet significant verschillend tussen meisjes en jongens. Neus- en oogklachten verschilden niet tussen kinderen met één allergie of met meerdere allergieën, maar de symptomen waren significant lager bij kinderen die geen allergie hadden. Meerdere allergieën komen vaak voor bij kinderen met allergische rhinitis in de huisartsenpraktijk. De ernst van de klachten zijn hetzelfde bij kinderen die een of meerder allergieën hebben. De beslissing voor be-

handeling van allergische rhinitis zou gebaseerd moeten zijn op een goede anamnese en allergietesten.

Hoofdstuk 8 bespreekt de belangrijkste bevindingen in dit proefschrift. De beperkingen van het onderzoek en de implicaties voor de huidige praktijk en toekomstig onderzoek worden besproken. Toekomstige studies zouden gerandomiseerde placebogecontroleerde dubbel-blinde studies moeten zijn voor het vinden van de optimale en veilige dosis en ook de optimale duur van de behandeling met sublinguale immunotherapie. De verbetering van de kwaliteit van leven van allergische kinderen en de therapietrouw zouden belangrijke aanvullende uitkomstmaten moeten zijn.

De bevindingen in dit proefschrift zullen hopelijk bijdragen aan het vinden van een mogelijke plaats voor een behandeling met sublinguale immunotherapie bij kinderen met allergische rhinitis in de Nederlandse eerstelijns gezondheidszorg.

List of abbreviations

AdolRQLQ	*Adolescent Rhinoconjunctivitis Quality of Life Questionnaire*
AR	*allergic rhinitis*
ANCOVA	*analysis of covariance*
ANOVA	*analysis of variance*
AMSTAR	*assessment of multiple systematic reviews*
ARI	*Allergic Rhinitis and Its impact on Asthma*
BU	*biological units*
CONSORT	*Consolidated Standards Of Reporting Trials*
FeNO	*Fractional exhaled Nitric Oxide*
GA2LEN	*Global allergy and asthma European network*
GINA	*Global Initiative for Asthma*
GP	*general practitioner*
HDM	*house dust mite*
HRQL	*health related quality of life*
ISAAC	*International Study of Asthma and Allergies in Childhood*
LNIT	*local nasal immunotherapy*
PRQLQ	*Paediatric Rhinoconjunctivitis Quality of Life Questionnaire*
RCT	*randomised controlled trial*
SCIT	*subcutaneous immunotherapy*
SIT	*allergen-specific immunotherapy*
SLIT	*sublingual immunotherapy*
STARDROP II	*sublingual immunotherapy in youngsters with allergic rhinitis, a double-blind randomised controlled study with house dust mite allergen*
WAO	*World Allergy Organisation*

Dankwoord

Het dankwoord van een proefschrift. Volgens mij meestal het eerste hoofdstuk dat wordt gelezen in een proefschrift. En ik moet toegeven dat ik het ook meestal doe. Het schrijven van het dankwoord betekent ook dat de voltooiing van mijn proefschrift in zicht komt. Ik heb met veel enthousiaste mensen samengewerkt, die hun bijdrage hebben geleverd aan het tot stand komen van dit onderzoek en ook mijn proefschrift. Een aantal wil ik hier apart benoemen.

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door mijn huisbezoeken, maar natuurlijk ook voor het luisteren naar mijn meestal onbegrijpelijk verhalen over analyses, artikelen, druppeltjes onder de tong.

Mijn " studie" is klaar!

Astrid, Marjolein en Lottie, we go way back. Vanaf onze HAVO periode tot nu, hebben we al het een en ander meegemaakt; van verschillende studies naar huwelijk en kinderen. Veel gelachen, soms een traan, maar vooral veel lol. Goede oude tijden herleven! Bedankt voor jullie vriendschap en natuurlijk twee keien van paranimfen aan mijn zijde.

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Anton, bedankt voor je nuchterheid, geduld en liefde, al meer dan 14 jaar lang. Ik kan er niet meer van maken! Onze kerel en meid, Roy en Jolein zorgen ervoor dat elke dag wel een klein feestje is.

Cindy

Curriculum Vitae

Cindy de Bot is geboren op 13 maart 1980 te Nispen. Na het behalen van haar HAVO diploma aan het Gertrudis College in Roosendaal, begon zij in 1997 aan de opleiding HBO- Verpleegkunde aan de Fontys Hogeschool Eindhoven.

In 2001 haalde ze haar Bachelor diploma en is daarna direct begonnen met de opleiding Gezondheidswetenschappen aan de Universiteit Maastricht.

In 2003 behaalde ze haar doctoraal examen van de richting Public Health and Prevention. Tijdens haar afstudeerproject onderzocht ze de kwaliteit van onderzoek vanuit het patiënten perspectief bij een fertiliteitbehandeling in het St. Elisabeth Ziekenhuis Tilburg. Dit onderzoek heeft geleid tot de ontwikkeling van een QUOTE (QUality Of care Through the patient's Eyes) vragenlijst. Tijdens deze opleiding heeft zij gewerkt als verpleegkundige in het Academische Ziekenhuis Maastricht en andere werkvelden van de gezondheidszorg.

In november 2003 is Cindy gaan werken bij Stichting Groenhuysen. In juli 2005 startte zij haar promotieonderzoek: Sublingual immunotherapy with house dust mite allergen in children with allergic rhinitis: randomised double-blind placebo-controlled trial bij Afdeling Huisartsgeneeskunde van het Erasmus MC in Rotterdam. Deze studie heeft geleid tot dit proefschrift. Sinds januari 2011 werkt Cindy als adviseur in Maasstad Ziekenhuis Rotterdam.

Cindy woont samen met Anton Hooijdonk en hun kinderen, Roy (2007) en Jolein (2010) in Wouw.

PhD Portfolio

COURSES

GCP course Good Clinical practice, ICH-training en advies , 2006	24 hours
Paediatric Drug Research, NIHES, 2006	15 hours
Epidemiologisch onderzoek: opzet en interpretatie, EPIDM VUmc, 2006	40 hours
Biomedical English Writing and Communication, Erasmus MC, 2007	40 hours
Principes van epidemiologische data-analyse, EPIDM VUmc, 2008	40 hours
Methodologie van patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen, ZonMw, 2009	8 hours

PRESENTATIONS

Pediatric Joint Meeting EAACI/ERC, 2007 Poster presentation	16 hours
DRSA Dutch Research School of Allergology, 2008 Poster presentation	16 hours
Dutch College of General Practitioners (NHG) Congress, 2008 Poster presentation	16 hours
COPD & Astma Huisartsen Advies Groep CAHAG Congress, 2009 Oral presentation	20 hours
Dutch College of General Practitioners (NHG) Congress, 2010 Poster presentation	16 hours
COPD & Astma Huisartsen Advies Groep CAHAG Congress, 2011 Two oral presentations	40 hours
Nederlandse Vereniging voor Allergologie (NVvA), 2011 Two oral presentations	40 hours

TEACHING

Evidence Based Nursing , 2009 Hogeschool Rotterdam , Students Bachelor Nursing	80 hours

Appendices

APPENDIX I SEARCH STRATEGIES

The search strategy for PubMed was:
("immunotherapy"[MeSH Terms] OR "immunotherapy"[All Fields] OR "Desensitization"[All Fields]) OR "Desensitisation"[All Fields] AND (rhinoconjunctivitis[All Fields] OR ("rhinitis, allergic, seasonal"[MeSH Terms] OR ("rhinitis"[All Fields] AND "allergic"[All Fields] AND "seasonal"[All Fields]) OR "seasonal allergic rhinitis"[All Fields] OR ("hay"[All Fields] AND "fever"[All Fields]) OR "hay fever"[All Fields]) OR (perennial[All Fields] AND ("rhinitis"[MeSH Terms] OR "rhinitis"[All Fields])) OR (allergic[All Fields] AND ("rhinitis"[MeSH Terms] OR "rhinitis"[All Fields]))) AND ("2000/01/01"[PDAT] : "2008/12/31"[PDAT] AND English[lang] AND (Meta-Analysis[ptyp] OR Review[ptyp])) AND English[lang]

The search strategy for Embase was:
('rhinoconjunctivitis'/exp OR 'perennial rhinitis'/exp OR 'hay fever'/exp OR 'allergic rhinitis'/exp) AND ('active immunization'/exp OR 'immunotherapy'/exp OR 'desensitization'/exp) AND [english]/lim AND [humans]/lim AND [embase]/lim AND ('meta analysis':it,it OR 'review':it,it AND [2000-2008]/py)
The search strategy for the Cochrane Library was:
"(immunotherapy OR desensitization) AND (rhinoconjunctivitis OR allergic rhinitis OR hay fever) in title, abstract or keywords

APPENDIX II AMSTAR WITH ADDITIONAL INFORMATION PER ITEM

AMSTAR

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

9. Were the methods used to combine the findings of studies appropriate?
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

10. Was the likelihood of publication bias assessed?
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

11. Was the conflict of interest stated?
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable