Chapter Two Outline of the study

1. PREFACE

The studies described in this thesis are all part of DUMAS, the **DU**tch **M**ite **A**voidance **S**tudy. The goal was to study the effect of encasings on allergic symptoms in house dust mite allergic patients. So far, various studies have been performed to evaluate the effect of impermeable covers, all dedicated to asthma and AEDS (atopic eczema/dermatitis syndrome).[1-24] No study has ever been performed to the effectiveness of encasings in patients with allergic rhinitis;[25-28] this is even more surprising considering that rhinitis is by far the most prevalent disorder of the atopic syndrome. Therefore, a trial was warranted.

Secondly, although many allergologists feel that they hardly see patients with only allergic rhinitis or asthma or AEDS, actual figures of the prevalence of allergic rhinitis in patients with asthma or AEDS are scarce.[29-32] The DUMAS study offered the opportunity to evaluate the comorbidity in the Dutch house dust mite allergic population. It made it possible to study the effect of rhinitis and comorbid associations on quality of life as experienced by allergic patients.[33] The design of the study and the instruments used to measure the effect of the encasings both objectively and subjectively, are described below.

2. SETTINGS AND SUBJECTS

2.1 Settings

The study was initiated by three University Hospitals – the Erasmus Medical Centre of Rotterdam, department of Allergology, the University Medical Centre of Utrecht, department of Dermatology, the University Hospital of Groningen, department of Allergology, and Sanquin, department of Immunopathology in Amsterdam. The heads of department, respectively, Dr. R. Gerth van Wijk, Prof. dr. C.A.F.M. Bruijnzeel-Koomen, Prof. dr. J.G.R. de Monchy and Prof. dr. R.C. Aalberse, were project leaders of the study. Each patient centre (Rotterdam, Groningen, Utrecht) had a research physician and a research nurse to carry out all necessary measurements. Blood and dust samples were centrally processed at Sanquin in Amsterdam.

The study was financed by NWO-SGO, the Dutch Scientific Organisation to stimulate medical research. Separate financial support for the quality of life studies was given by the Dutch Asthma Foundation. HAL, the Haarlem Allergen Laboratories, provided all encasings, including the placebo encasings. The Medical Ethical Committee of all participating University Hospitals approved of the study.

2.2 Periods of research

All patients were studied for one year. Measurements for the first cohort took place in September until December 1997 (baseline measurements), January until March 1998 (first follow up visit) and September until December 1998 (second follow up visit); the second cohort came for baseline visits from September 1998 until December 1998 and for follow up visits from January until March 1999 and September until December 1999. The reason these periods were chosen were twofold. The highest concentrations of house dust mite in the Netherlands are found in autumn and early winter, corresponding with September until December; the pollen season ends in the beginning of September and usually does not start until the end of February. By inviting pollen allergic patients outside these periods we could prevent bias by pollen allergic symptoms.

2.3 Subjects

Patients taking part in the study were partly patients of the forementioned University Hospitals, from the departments of Allergology (Rotterdam and Groningen), Dermatology, ENT and Pulmonology. Other patients originated from general hospital clinics or practices of general practitioners or had responded to an advertisement in lay press.
To be able to participate in the study, a patient had to meet the following criteria

- Age between 8 and 50 years
- Allergic to house dust mite, assessed by either
    - a skin test with a ratio of allergen and histamine weal diameter ≥ 0.7[34,35] or
    - an allergy blood test with RAST class 2 or higher
- The dust sample of the bare mattress had to contain ≥ 200 nanogram Der P1 and/or Der F1 per gram dust, respectively the major allergens of Dermatophagoides Pteronissynus and Farinae
- Allergic rhinitis defined by clinical features and classical history of rhinitis being nasal obstruction, sneezing, watery discharge for at least one year and a positive nasal provocation test with house dust mite allergen (described below) and/or
- Allergic asthma defined by a one year history of asthma, physician based diagnosis or use of inhalation steroids, reversibility of 9% or more,[36] or PC_{20} methacholine of 9.8 µg or less[37] and/or
- AEDS (atopic eczema/dermatitis syndrome) defined by the criteria of Hanifin and Rajka plus a Leicester sign score, a scoring system for disease activity, of 6 points or more and an extent of > 1% [38-40]

Patients were not allowed to have pets at home if they were allergic to the very pet. Anatomical disorders of the nose, pregnancy or breastfeeding, daily use of oral inhalation steroids ≥ 1600 µg /day (adults) or ≥ 800 µg /day (children), oral steroids, cyclosporin, regular use of antibiotics for upper or lower airway infection or regular use of oral steroids for exacerbation of asthma were considered as exclusion criteria. Furthermore, patients were not allowed to move or change the furnishing in their house (e.g. new mattress or curtains in the bedroom or new carpet in the house) during the research period.

3. DESIGN

3.1 General

The study was designed as a double blind, placebo controlled trial with a follow up of one year in which three visits were scheduled, one baseline visit and two follow up visits.
In a pre-baseline visit, one of the research physicians took the allergic and general history of the patient; next, an examination of the nose was done to exclude anatomical disorders. Skin tests and/or blood tests to assess sensitisation to house dust mite, tree, grass and weed pollen, and cat and dog were performed. Supplementary skin tests were carried out, if a patient had other animals at home. Afterwards, if a patient was still considered eligible, he or she was given the materials to take a dust sample of their mattress. If the result of the sample was according to the preset criteria (> 200 ng Der P1 or Der F1 per gram dust), the patient could be included in the randomisation procedure.

3.2 Randomisation and Blinding

Eligible patients were randomly allocated to receive placebo or active encasings for all mattresses, pillows and duvets in the bedroom; assignments to placebo or active cover were made using a central computerised randomisation schedule at the Julius Centre, Utrecht. After randomisation and assignment a research number, initials, dates of birth and the measures of the bedding were faxed to the Julius Centre. Research number and bedding measures were sent by the Julius Centre to the manufacturer of the encasings, HAL, Haarlem, the Netherlands. A cardboard box, containing all encasings, was sent to the research center, with the research number written on the box. Patients took the box home and opened it in the absence of research staff. Encasings of pillows, duvets and mattresses were applied after baseline dust collection by the patient. Dust sampling was performed by trained students who did not participate in clinical measurements to ensure blinding.

3.3 Baseline Visit

A baseline visit consisted of three visits. At the first visit, a reversibility test was performed. Also, a daily symptom score for nasal symptoms was handed out and instructions how to fill it in were given. Patients were asked to keep this daily symptom score for 14 days. After 14 days patients came to the hospital for the second and third baseline visit. All nasal medication was stopped to avoid bias: oral antihistaminics were stopped 3 days and nasal sprays 2 to 4 weeks before starting the daily symptom score to ensure a long enough wash out period. Patients were given acrivistine, 1 to 3 times a day, taken as needed, as rescue medication during this period although the use of rescue medication was discouraged to obtain unbiased symptom scores. The use of acrivistine had to be noted in the daily symptom score.
At the second visit, patients had to fill in a general quality of life questionnaire (SF-36), 2 disease specific quality of life questionnaires (asthma quality of life questionnaire and Marburg questionnaire for eczema) and visual analogue scales (one for asthma, two for eczema). A methacholine provocation test was performed to assess lung function. Skin testing for adults consisted of both skin prick test and intracutaneous test with house dust mite, children underwent the prick test. In both adults (defined as patients ≥ 18 years) and children (defined as age 8 to 17 years) a atopy patch test was performed with house dust mite. The following day, all adults underwent a second lung function test with adenosine.
Nasal provocation (as described below) was performed in both children and adults; nasal lavage was done in patients ≥ 18 years. Before nasal provocation, patients had to fill in a disease specific questionnaire (rhinitis quality of life questionnaire) and visual analogue scale for nasal complaints. After this visit a trained student visited the patient at home to take dust samples of the mattress, bedroom and living room (as described below). After these dust samples were taken, the patient was allowed to apply the encasings for mattress, pillows and duvet.

3.4 First follow up visit

The first follow up visit took place 4 months after baseline visits. It consisted of two visits: the first one to acquire the daily symptom score, the second one 14 days later, to hand in the daily symptom score and to fill in all quality of life questionnaires (SF-36, Marburg questionnaire, AQLQ and RQLQ) and visual analogue scales for complaints of asthma, rhinitis and eczema. All skin tests as described above were repeated; after this visit patients were visited again by one of the students to obtain dust samples.

3.5 Second follow up visit

The second follow up visit took place 12 months after baseline measurements. This visit was an exact copy of the baseline visit; the reversibility test was omitted in this visit.

4. ENDPOINTS OF THE STUDY

4.1 General

All measurements described below were chosen specifically to assess allergic rhinitis. Asthma was evaluated by means of peakflow measurements, reversibility, provocation with methacholine and adenosine, blood eosinophils, a visual analogue scale for asthma symptoms and the Asthma Quality of Life Questionnaire (thesis Z. Tempels-Pavlica, M.D., to be published). Endpoints for AEDS were the Leicester Sign Score, atopy patch tests with house dust mite, intradermal and skin prick test with house dust mite, a VAS for itching and sleeplessness and the Marburg questionnaire (thesis A.J. Oosting, M.D., PhD., Effect of encasings on allergen load, clinical variables and quality of life variables within an atopic population, Utrecht, 2002).

4.2 Primary Endpoint

Visual analogue scale (VAS)

A visual analogue scale is a horizontal line of 100 mm; the left end or the zero represents no complaints at all whereas the right end or the 100 represents very serious complaints. A patient is asked to evaluate his or her complaints of the past 2 weeks and represent the awarded score by a vertical line on this horizontal scale. By assessing for example the VAS before and after the use of medication, the effect of the medication can be estimated and compared to placebo. The VAS is widely used to evaluate complaints in both allergic and non allergic research. Surprisingly enough, validation studies have been done only for the assessment in pain research.[41,42] In allergy research however, it has proven to function adequately in studies of Blom and Varney.[43] [44] The VAS was chosen as our primairy endpoint for a number of reasons. The VAS is easy to use, it takes little time to fill in, it has already taken its place in research and it could be a simple, useful tool in daily practice for a clinician to evaluate therapeutic interventions. Disadvantage of the VAS is that it requires an adequate assessment of his or her nasal complaints by the patient. This could be a problem in children but even for adults it can be difficult to recall the amount of complaints caused by the nose in the past week or fourteen days.

4.3 Secundairy Endpoints

4.3.1. Rhinitis Quality of Life Questionnaire (RQLQ)

The RQLQ is a questionnaire developed by Juniper to evaluate complaints of allergic rhinitis.[45] Patients have to score 28 items comprising 7 domains: nasal symptoms (n=4), practical problems (n=3), non nasal symptoms (n=7), sleep disorders (n=3), (impairment of) activities (n=3), eye symptoms (n=4) and emotions (n=4) on a 7-point scale (0=not bothered, 6=extremely bothered). This questionnaire was chosen because it has proven its value in rhinitis oriented research with special versions for adults, adolescents and children.[45-53] Disadvantage of this and any other disease specific questionnaire is, that other diseases can't be taken into account. This hampers the comparison between the different expressions of the atopic syndrome regarding quality of life.

4.3.2 SF-36

General questionnaires like the SF-36 have been used in many studies to evaluate the effect of treatment. Their advantage is that they cover multiple aspects of daily life and both mental and physical well being. For the Netherlands, a Dutch version was developed by Aaronson and co-workers.[54] SF-36 consists of 36 questions divided over 8 subscales, including physical health subscales - physical functioning, role physical functioning, bodily pain and general health –and mental health subscales - mental health, role mental functioning, social functioning and vitality. Questions are stated in both yes/no form and multiple choice. A sum score is calculated for each subscale and transformed to a percentage of the total possible score. High score indicates good quality of life, while low score indicates low quality of life. The reliability in two general population samples as reported by Aaronson using Cronbach's α varied from 0.76 to 0.92 while the item discriminant validity varied from 0.09 to 0.64. As mentioned above, SF-36 covers multiple aspects of life and it is not designated to one disease or group of disorders. Therefore, it has an major advantage over a disease specific questionnaire: using this questionnaire makes it possible to compare the quality of life of patients with more than one atopic disorder to patients with mono-allergic disease or to compare the different combinations. Since little is known about the effect of multiple atopic disorders on quality of life in comparison to mono-allergic disease, we integrated the SF-36 in the study.

4.3.3 Daily symptom scores

Daily symptom scores or diaries are used frequently in research.[9,55,56] The patient records the presence and severity of the symptoms of his or her disease for a limited period of time on a daily basis. The advantage over a questionnaire is that a questionnaire is a snapshot and therefore more sensitive for the complaints and mood of the moment. In a day to day score the scores for the various

complaints are averaged. This would hopefully lead to a more reliable representation of a patients symptoms. Although simple in design, the major drawback is obvious: it requires the discipline to fill in the daily symptom score at a daily basis indeed; considering that men (and women) do tend to forget things, one can wonder if such discipline can be yielded for 14 days. The daily symptom score for nasal complaints was included to explore its behaviour compared to the other rhinitis specific quality of life measurements, the VAS and RQLQ. Patients were asked to record nasal symptoms during 14 days on a daily basis. Nasal obstruction, nasal discharge and sneezing were recorded on a 0-3 scale (0=none, 1=mild, 2=moderate, 3=severe). Scores were summed and the average of 14 days was reported as daily nasal score. Patients with a daily symptom score filled in less than 12 days were excluded from analysis.

4.3.4 Nasal provocation test

Nasal provocation tests are used to evaluate two problems: one can perform a provocation with allergen to assess if a person reacts to the very allergen and if so, how serious this reaction is. The second goal of nasal provocation is to establish the presence and severity of nasal hyperreactivity by means of for example histamine, methacholine or capsaicin. Both forms of provocation are mainly used to evaluate the effect of medication and to unravel the cells and mediators taking part in the allergic reaction in the nose.

From studies in grass pollen allergic patients is known that after exposure to grass pollen in nasal provocation outside the season, less pollen are required the next time to evoke symptoms (priming effect). Patients experience the same in the grass pollen season: in the course of the season, less pollen are required to evoke the same amount of complaints. After the grass pollen season, the nasal complaints disappear and the situation returns to the point of departure (or the start of the season). As described in the previous chapter, this could be explained by the amount and nature of the cells that invade the nasal mucosa after allergen exposure. In this study provocation with allergen was chosen for a number of reasons. Our first reason was the use of the nasal provocation as a conformation of the clinical assessment of allergic rhinitis. Since perennial allergic rhinitis can be difficult to assess we used the provocation with allergen as a way to ensure that nasal complaints were really evoked by insufflation of house dust mite allergen. Secondly, we wanted to use the nasal provocation as a way to evaluate the effect of encasings. The assumption was that reduction of the exposition to the house dust mite allergen could perhaps lead to a process similar to the grass pollen patient after the end of the season. We hoped that the reduction of exposure would lead to a less prominent presence of inflammatory cells and subsequently to less severe symptoms after provocation with allergen.

The actual performance of the provocation has previously been described in detail by de Graaf- in ‘t Veld.[57-59] The same procedure was followed in this study. Before nasal provocation started each patient had to acclimatise 30 minutes in the room where nasal provocation took place.

After this period, a composite symptom score according to Lebel et al comprising the number of sneezes during those 30 minutes, nasal stuffiness, itching of the nose, eyes, palate and ears, rhinorrhea and post nasal drip was obtained.[60] Patients received one puff of PBS in both nostrils by insufflation of a nasal spray with a fixed dose of 0,125 ml/puff. After 10 minutes the number of sneezes, itching, stuffiness of the nose, rhinorrhea and post nasal drip were scored just before the challenge with the first dose of house dust mite of 100 BU/ml. Again, after 10 minutes all 5 items were scored and the next dose of 1000 BU/ml was given. The same procedure took place for the third and last dose of 10.000 BU/ml. The composite score was also obtained 20 and 30 minutes after the last dose.

4.3.5 Dust sample measurement

Dust samples from mattresses were collected by a standardised procedure. The mattress of the patient was vacuum cleaned for 5 minutes with a vacuum cleaner (Rowenta RS 005 Dymbo 1200 Watt) containing a 20 µm filter paper in a filter chamber (ALK, the Netherlands). At baseline samples were obtained from the mattress covered with sheets and pillows. A second sample was taken from the mattress itself. After 4 and 12 months, mattress samples were obtained from the mattress covered in encasings and sheets. Samples were stored at -4 ºC in a box containing silica gel to keep the samples free from water until transportation to the Laboratory of Allergy, Central Laboratory of the Blood Transfusion Service, Amsterdam, where the samples from all three participating centres were processed.[24]

5 RESEARCH QUESTIONS

The study was designed to try and answer the following questions

1) What is the effect of impermeable covers on both objective and subjective parameters in patients with allergic rhinitis and house dust mite allergy?
2) What is the prevalence of allergic rhinitis in patients with asthma and AEDS and house dust mite allergy?
3) What is the effect of rhinitis and comorbid associations on quality of life measured by general and disease specific questionnaires?

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