Chapter 8 General discussion and conclusions

This thesis describes the Dutch study to the effect of impermeable encasings in patients with allergic rhinitis and house dust mite allergy. The study was designed to answer three 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?

1. EFFECT OF ENCASINGS IN HOUSE DUST MITE ALLERGIC PATIENTS

1.1 Effect of encasings in allergic rhinitis

Our major goal was to assess the effect of impermeable covers on symptoms of allergic rhinitis. The available literature on the effect of intervention in patients with allergic rhinitis is scarce; in a review for the Cochrane library Sheikh and Hurwitz concluded that only four trials satisfied the inclusion criteria – being randomised and controlled trials – but they were small and of poor quality.[1] Reisman evaluated the use of HEPA filters in a group of 40 patients with allergic rhinitis and/or asthma for a period of eight weeks in a double blind, cross-over study.[2] Kniest and Bernstein studied the effect of acaricides.[3,4] The only study with partial encasings was done by Moon; he wrapped mattresses in vinyl covers.[5] The studies in AEDS (atopic eczema/dermatitis syndrome) show more or less the same picture. Only six studies have been performed to the effect of encasings.[6,7] Best known is the study of Tan in 48 children and adults with atopic dermatitis.[8] In both the placebo and intervention group, the skin improved. Der p1 in dust samples from the mattress also decreased in both groups. The decrease after 12 months in eczema scores and Der p1 in mattress was significantly larger in the treatment group. Tan used three treatment regimes at a time, bed covers, acaricides and a high filtration vacuum cleaner. The drawback of this design is that is does not permit us to the clinical effect of the separate measures. Gutgesell also combined encasings with acaricides. He could detect a significant reduction in mite allergen exposure but not in the severity and extension of the eczema.[9] Holm found a significant improvement in patients using active covers. His patient group comprised subjects with and without house dust mite sensitivity. Moreover, at the start of the study detectable levels of HDM allergen in the mattress sample were present in only 36.5% of the active group and 11% of the placebo group. Surprisingly, both patients with and without mite sensitivitiy equally benefitted from the covers.[10] The most recent trial in atopic dermatitis was a double blind, placebo controlled, randomised trial by Oosting which was also a part of the Dutch Mite Avoidance Study.

He could not demonstrate any change in severity or extent of the atopic dermatitis, neither in VAS, intracutaneous skin test, patch test, blood eosinophils, total and specific IgE.[11]

The majority of studies have been performed in patients with allergic asthma and house dust mite sensitivity. As discussed before, the studies are difficult to compare. The studies in the seventies and early eighties of the last century used plastic covers, effect on allergen was measured by an absolute mite count or follow up period was very short.[12-16] Some studies lacked the use of placebo groups or placebo covers.[17,18] In a number of studies the investigators could not detect a difference in mite exposure the placebo and intervention group after the intervention period.[18-20] Only a few well designed studies (double blind, placebo controlled, randomised trial, adequate measures to prevent bias by pollen and/or animal sensitisation, a sufficiently long follow up period) were able to show a significant decrease in allergen exposure.[21-23]

In our study we fulfilled most of the criteria suggested by Sheikh and Hurwitz in the Cochrane review: in their article they recommend to set up studies that are pragmatic, adequately powered, with uniform inclusion criteria, and with a follow up period longer than 6 months. Outcome measures should include changes in validated generic and disease specific quality of life measurements, school/work absenses, other medication usage, satisfaction and cost-effectiveness of treatment.[1] Our study was designed as a double blind, placebo controlled trial. We performed a power analysis to ensure we included enough patients to achieve relevant results. We had preset criteria a patient had to fulfill to allow participation in the study and patients were followed for 12 months. It was a pragmatic trial, since we included patients with all expressions of the atopic syndrome and a broad variety of severity of symptoms. We did not measure absence from school or work and since we let patients stop all nasal medication, we did not measure change in medication use. Also, we did not perform a cost-effectiveness analysis.

The outcome measures we used were partly validated; SF-36 and RQLQ have been extensively validated, whereas outcome measures as daily symptom scores and VAS, nasal provocation tests and Der p1 measurements appeared to be responsive to interventions in many clinical trials. So, in conclusion, this study fulfills most of the criteria Sheikh and Hurwitz proposed. In addition, we took other precautions to ensure optimal conditions: to avoid bias due to pollen allergic complaints by planning visits outside the pollen season. Pet keeping was not allowed unless skin test and/or RAST was negative just as moving or making changes in the house for the period of the study. Intervention and placebo covers were tested in advance to ensure good quality of both: Our placebo covers provided a 15% barrier compared to a 98% barrier by the intervention covers.

After 12 months of intervention, a threefold reduction in Der p1 and Der f1 levels was achieved in mattress dust samples obtained from the patients in the intervention group. In the placebo group a small but insignificant reduction of 18% was seen. Our first conclusion was that impermeable covers diminish exposure to house dust mite allergen. Unfortunately, this reduction was not accompanied by a signicant difference between intervention and placebo group on VAS, daily symptoms or nasal provocation test in the study group.

Assuming we performed the trial correctly, did we select the right patients? Perhaps it would have been wiser to choose a group more consistent in age, only sensitised to house dust mite and suffering from allergic rhinitis only. For example, the study of Halken was performed in children with asthma and house dust mite allergy, with no other allergies allowed.[23] She found that in the group with impermeable encasings the dose of inhaled steroids could be reduced. Although elegant in design and well performed, the drawback of this study is that the results are not applicable to quite a number of other allergic patients. Our patient group comprised both children and adults, suffering from rhinitis with or without asthma and/or AEDS, characterised by varying degrees of disease severity. Otherwise stated an adequate representation of the patients seen by specialists and general practitioners in the Netherlands. Our results are therefore valid for the house dust mite allergic patient in general while the results of studies in selected patient groups are not necessarily applicable to the remaining allergic patients. The negative results in this group, however, do not necessarily exclude good results in more selected groups. We tried to identify possible subgroups in which mite avoidance could be of advantage. Firstly, in analogy with the Halken study, we analysed the results in the group aged 18 years or younger. We also performed separate analyses for the people with the most severe complaints, defined as the upper quartile of the VAS, to see if they had benefited from the covers. Our third subgroup consisted of the patients with the highest exposure to house dust mite allergen, defined as a Der p1 and Der f1 concentration of 5 microgram/gram dust or higher, under the assumption that more room for improvement would exist in this group. We defined a fourth subgroup excluding patients sensitised to other allergens than house dust, also in analogy with Halken, and a fifth, consisting of highly sensitised patients (RAST class 4, 5 or 6). Finally, we selected the patients with wall to wall carpets or rugs in bed room, living room or both as opposed to patients with smooth surfaces in these rooms. In all 6 subanalyses, results were the same as the primairy analysis: the VAS in both intervention and placebo group improved but no significant difference between both groups was seen. Ideally, analyses with combinations of “risk factors” should have been done, like children with high exposition or children with a monoallergy. Our group was not large enough to permit such analyses but it would be interesting to carry out a study in such groups in the future. A regression analysis might have been interesting to investigate the possibility of an interaction effect.

1.2 Effect of encasings on general quality of life in atopic patients

Our study was focussed on patients with allergic rhinitis. The use of the SF-36, a generic quality of life instrument, however permitted us to broaden our objectives and to study adults with house dust mite allergy irrespective of the organ involved.

We choose to perform an analysis by means of a random regression modelling (RRM) analysis for continuous data because in our opinion RRM was more suitable. RRM is more flexible than multiple regression analysis since for instance variances and covariances are allowed to vary in time and missing data from patients does not lead to exclusion. In this analysis sex and asthma had a

significant and considerable effect on the physical sumscore of the SF-36; the time trend was significant but the actual effect was nil. In the emotional sumscore only sex had a significant effect. We saw no effect of treatment, age, AEDS or rhinitis on SF-36 sumscores. The lack of effect of the diagnoses on the SF-36 sumscores was a confirmation of the results seen on SF-36 subscales.[24] The lack of effect of treatment on disease specific parameters for rhinitis we already demonstrated in the participating rhinitis patients of the study, but this analysis indicates that irrespective of the organ involved, encasings do not improve quality of life, despite their good reducing effect on mite exposure.[25]

1.3 Effect of encasings – possible explanations for the lack of effect

Although in theory allergen avoidance should improve allergic symptoms, we were not able to demonstrate any effect of the encasings on outcome parameters with exception of the decrease in allergen exposure. To explain the lack of success, one possibility is that the baseline level of mite exposure was too low to obtain a reduction sufficient for clinical improvement. Patients entering a mite avoidance study are prone to self selection; they are interested in the topic and are probably more willing to implement mite avoidance measures.

Our baseline levels compared to other international studies were indeed low, but they were in line with the Dutch PIAMA study and are therefore representative for the Dutch situation in general; a subanalysis in the highest quartile of the concentration of mite allergen in mattress dust did not alter results.[26,27] A second possibility is, that mite avoidance is only useful in young children in which allergic inflammation has not been settled yet. In asthma, it is well accepted that structural changes occur in addition to inflammatory infiltration.[28] This could explain the positive results of Halken since the mean age of her study group is probably lower than ours; she studied children in the ages 5 to 15 (mean unknown) while our children were 8 to 18 years old with a mean of 12.5 years. In a younger age group with less advanced disease allergen avoidance could lead to regression of inflammatory processes and prevention of remodelling. The question is whether this is also true for the upper airways. Reports on remodelling changes in allergic rhinitis so far are conflicting.[28-31] If it really does exist, it would be interesting to investigate the effect of strict avoidance in patients with rhinitis in which remodelling has not taken place yet.

A third possibility is that the reduction in the bedroom, although significant, is simply not sufficient to achieve clinically relevant results. Perhaps, the amount of allergen that a patient encounters in daily life outside the bed is too high to be overcome by the single intervention with encasings. Moreover, theoretically other avoidance measures could mask the effects of encasings. From literature however, it is known that environmental control advice is not structurally followed.[32-35] Joseph found that supplying encasings to patients improved the use of encasings in comparison to patients who had to purchase the encasings themselves – 90 vs 50% - but observed rate of using other dust mite avoidance measures was only 50% in both groups.[33]

Bearing these results in mind, it is unlikely that the advices we gave our patients – regular vacuum cleaning, washing bed linen at 60°C and clean, ventilate and heat the house on a weekly basis – had a major influence on our results, as suggested in a editorial by Platts-Mills.[36] The slight decrease in allergen in the samples of bedroom floor and living room floor confirm this. Besides, it is still a matter of debate whether vacuum cleaning and (mechanical) ventilating are truly contributing to the reduction of house dust mite.[37-41]

One could argue that it is more logical to assess the total personal exposure to mite allergen by means of a personal sampler, as recently suggested by Tovey. According to the outcome of the samplers, measures to control mite allergen exposure could be taken.[42] But even in the ideal situation that a patient is not exposed to mite allergen at home, exposure outside the house will still continue. Der p1 concentration in dust is less in public places compared to domestic dwellings but exposure in for instance hotels, children day care and schools will occur.[43] Moreover, as we saw in our population, the majority of patients was also sensitised to pollen and/or animals. According to the latest figures, 27% of the Dutch families keep a cat, 21% has a dog, 9% keeps a bird and 9% a rabbit. Earlier research showed that dust samples taken in public places and public transport contain both cat and dog allergen.[44,45] These data imply that it is impossible to avoid animal allergen just as it is impossible to avoid tree and grass pollen walking outside in spring or summer. Apart from other allergens, endotoxines in dust may also lead to respiratory symptoms, whereas it is conceivable that encasings do not diminish endotoxin levels. The question remains whether it is realistic to expect reduction of symptoms even after total reduction of house dust mite allergen at home if exposure to allergen outside the home remains, especially in multisensitised patients.

2. PREVALENCE OF COMORBIDITY AND ITS EFFECT ON QUALITY OF LIFE

Our second major goal was to study the prevalence of allergic rhinitis in patients with allergic asthma and AEDS and the effect of comorbidity on quality of life. The number of studies regarding comorbidity are not abundant but this topic has gained more interest recently; most studies however, are based on self administered questionnaires, some lacking (skin) tests to confirm sensitisation and no studies so far have included AEDS (atopic eczema/dermatitis syndrome). In this study we had the opportunity to obtain figures regarding the presence of rhinitis in patients with asthma and/or AEDS. Because the diagnostic process in earlier studies was not always complete, a diagnosis of rhinitis, asthma or AEDS was only made if a patient fulfilled a series of preset criteria. The total percentage of patients with comorbidity was an impressive 53%. After selection of patients with asthma we found, that 92% of the patients with asthma had perennial rhinitis; in the group of patients with atopic dermatitis 85% had nasal symptoms. After nasal challenge these figures were 84 and 79% respectively; nasal provocation apparently adds little if history taking and skin test or blood test are performed adequately. This supports the guidelines of the ARIA that a thorough history and a skin test or specific IgE in blood are sufficient to diagnose (perennial) allergic rhinitis.

The most important message however, is that comorbidity is a common phenomenon, not only in asthma patients but also in AEDS and probably far more common than most specialists realise. Our figures are higher than those in earlier studies in the seventies of last century[46-48]; other, more recent studies however, show the same picture.[49-52] The consequence for daily practice is that both specialists and general practicioners have to realise that the risk of multi organ involvement in an allergic patient is high and that they have to evaluate each possible affected organ and not just the subject of their specialty.

The last decades the influence of allergy on quality of life has also gained attention; several studies already showed that patients with rhinitis have lower scores on both SF-36 and RQLQ and improvement with therapy.[53,54] The effect of comorbidity is less well known. In this study we evaluated quality of life by means of SF-36 and RQLQ apart from classical outcome measures as VAS and daily symptom scores. The choice for these outcome measures was based on practical considerations. We wanted to evaluate the burden of disease across the borders of the different organs as well as the effect of comorbidity. Although disease specific questionnaires are very well equipped to evaluate the complaints concerning the specific organ, it is impossible to use them for a comparison between different diseases e.g. rhinitis and AEDS. For this purpose a general quality of life questionnaire was needed; this enabled us to compare the quality of life in patients with rhinitis, patients with asthma and patients with AEDS. Furthermore, it would also enable us to evaluate whether patients with mono organ involvement like rhinitis alone would experience a better quality of life than patients with multi organ involvement do. The disadvantage of a general quality of life questionnaire is that it is less sensitive to clinical important changes.[55] We therefore included the RQLQ, a validated quality of life questionnaire, to evaluate nasal complaints and in addition two non validated but much used instruments, the VAS and the daily symptom score. Although frequently used, the performance of these disease specific instruments has never been compared before in a trial.

We demonstrated a significant lower score on almost every SF-36 subscale in our study population compared to the Dutch norm group. The diagnosis appeared to be a rather insensitive predictor of quality of life: asthma patients had a significant lower score on Physical functioning and General health while rhinitis and AEDS had no effect at all. The high percentage of rhinitis patients (almost 90%) could be the explanation for the lack of effect of the diagnosis rhinitis; perhaps the number of patients without rhinitis was simply too low to evaluate the effect of rhinitis. A second reason could be that using a diagnosis to predict quality of life as assessed by SF-36 is incorrect; our patients expressed a broad variety of symptoms, from mild to severe. Perhaps the range was too broad to have predictive value with regard to quality of life scores. The visual analogue scales – a subjective measurement for the severity of complaints - for asthma and sleeplessness (the latter being highly associated with AEDS) were more closely related to the SF-36 subscales than the main diagnoses. The VAS asthma was significantly associated with all domains except Bodily pain and Mental health,

whereas the VAS sleeplessness was associated with all domains except Physical functioning and Role emotional functioning. These findings support our idea that the diagnosis is too crude and that an instrument like VAS, enabling a patient to estimate the severity of symptoms is more suitable to predict quality of life. In contrast to Leynaert we could not find a significant difference in SF-36 subscale scores in patients with rhinitis compared to patients with both rhinitis and asthma, although the scores did demonstrate a trend to be lower in the patient groups with comorbidity. Most likely, the difference can be explained by the higher patient numbers in the Leynaert study.[56]

A surprising finding was that, contrarily to our expectations, the severity of nasal complaints was negatively associated with comorbidity. It has always been assumed that comorbidity represents a more advanced state of the atopic syndrome and therefore may lead to more severe complaints. Our study showed the opposite: Patients with either AEDS or asthma appeared to experience less symptoms of the nose. It is possible, that asthma and AEDS have such an impact on the perception of nasal disease that concomittant nasal complaints seem relatively unimportant. The inverse relation between AEDS or asthma and nasal symptoms was not present in patients suffering from both AEDS and asthma; Perhaps the inverse relation between asthma and nasal complaints is clouded by the presence of AEDS.

The evaluation by means of both generic and disease specific questionnaires seems somewhat redundant; both are measurements for quality of life. We used as mentioned above the SF-36 to investigate whether comorbidity affects quality of life, while the RQLQ has been tailored to monitor the course of rhinoconjunctivitis during the trial. We were able to show that SF-36 and RQLQ have overlap but only in the non nasal domains. Although administration of multiple questionnaires may be time consuming, it is worthwhile to use both questionnaires since they cover different aspects of quality of life and offer different possibilities. Disadvantage of both instruments and the VAS is that they represent one moment in time like a snapshot. Moreover, the difficulty of the VAS is that it requires the ability to translate symptoms into a certain point between zero and hundred. One can wonder whether the younger population in our study was really able to perform this task. The advantage of the daily symptom score is that it is simple and easy to perform; however, it requires the discipline to fill it in at a daily basis. The best way to obtain truly reliable daily symptom scores would be a digital version that, beside the answers on the questions, also records the day and hour the patient fills in the questionnaire.

Are quality of life questionnaires sufficient to be used as single outcome measures in clinical trials? Most likely not. We know from earlier research by Juniper that the results of the test and retest of the RQLQ after a short period in a stable patient group are reliable and comparable. Studies in allergic patients with antihistamines or nasal sprays by means of quality of life questionnaires show improvement but these are also short term studies. The major problem is that questionnaires always reflect the mind of the patient of that certain time and moment and after a longer period it is possible that a patient has a different perception of the severity of complaints in the past, the so called

response shift.[57] Also, the outcome of the questionnaires may be influenced by distortion, faking good or faking bad.

In conclusion, we emphasise the importance of quality of life measurements in clinical trials. However, they should be included together with other, objective outcome measures.

3. FUTURE RESEARCH AND RECOMMENDATIONS

Research can answer questions but more frequently, it raises even more questions. This DUMAS study also leaves us with a few unsolved items. The first one is how to deal with allergen avoidance in daily practice. In general, the idea of allergen avoidance is still valid; what we must ask ourselves is whether environmental control is still the method of choice in house dust mite allergic patients and more specifically, whether the use of impermeable encasings is still something we should do. Otherwise stated, should we dissociate ourselves from prescribing them or should we continue to use encasings as a measurement of avoidance? In this study, we could not demonstrate favourable effects of the use of encasings. Nevertheless, to abandon the use would perhaps be too extreme a measure. It is very well possible that in highly selected groups, like the group of Halken, covering the bedding can have positive effects. Cloosterman observed in a group of patients with pulmonary complaints but without the diagnosis of asthma, that the patients with placebo encasings showed a deterioration in lung function after 20 weeks while the group using impermeable encasings had a stable lung function test throughout the study. Although 20 weeks is a short follow up period, the observation is very interesting; one could speculate that encasings could prevent or postpone the development of asthma. The study group of Halken consisted of very young children; perhaps the process of inflammation was still reversible in this population. The patients of Cloosterman did not fulfil the criteria for asthma although they did have pulmonary complaints. If this is also a group in which the inflammation process is still reversible, one could hypothesise that encasings can lead to improvement of or non worsening of airway complaints. It remains to be seen whether this is also true for atopic dermatitis. As stated above, it is also possible that the intervention as we performed it, was not extensive enough. Perhaps reduction in mite exposure by means of extending intervention to the entire house instead of restriction to the bed would have lead to improvement of symptoms. To address this issue a study design as has been used in the Manchester Asthma and Allergy Study (MAAS) might be worthwhile.[58] The MAAS is a primairy prevention project, set in a birth cohort study in which a nested intervention study in high risk children is executed. The intervention group has to follow a strict protocol including encasings for both parental bed and the bed of the newborn, a high filtration vacuum cleaner and Acarosan. Carpets are removed from the nursery, the floor is changed to a vinyl cushion floor and a hot washable toy is supplied. The placebo group only gets mite avoidance advices. So far, the children in the avoidance group have less respiratory symptoms like wheezing in comparison to the placebo group.[59] The future will tell whether these children will develop less sensitisations and expressions of the atopic syndrome.

The design of the study is an attractive one to apply to patients already sensitised to house dust mite and suffering from rhinitis, asthma or AEDS. The problem is that it is impossible to perform such a study in a double blind or even a single blind setting with the risk of bias in subjective outcome measures. Moreover, with such a design it is not possible to separate the effects of the different measures. Nevertheless, it would be interesting to investigate whether patients carrying out intervention measures in the entire house would show improvement compared to patients taking no avoidance measures or intervention measures in the bedroom only. A second possibility is to perform a study with personal samplers, in which the results of the sampler are translated into environmental control measures tailor made for the patient. Again, this could never be performed in a double blind setting but the advantage would be that the important sources of all relevant allergens – not just house dust mite, but every allergen that the patient is sensitised to – can be identified and adequate measures can be executed.

Still, this does not answer the question what to do with a house dust mite allergic patient sitting at your desk, asking his doctor whether he or she should use encasings. Are we going to tell this patient that he or she should buy them or that it is a waste of money?

Perhaps the most logical route to follow, awaiting further research, is to advise people who are highly motivated to adapt their house and habits, to carry out all measures to avoid house dust mite, like smooth surfaces, washing bed linen at 60 ^{0}C and regular dusting and vacuuming. They should also be told that strong evidence for the effect of mite avoidance is lacking but it is advised under the assumption that avoidance of allergen would logically lead to diminishment of symptoms. Secondly, optimal treatment with local and systemic medication is a necessity as is advice about environmental control if a patients house is not up to standard. In case of pets at home and a positive skin test or RAST, people should be advised to place the pet elsewhere. The possibility of immunotherapy should be considered and discussed with the patient.

As mentioned above, allergy is not a disease that affects just one organ, it is a multi organ disease. This was the first study that included AEDS; further studies are warranted to the prevalence of comorbidity. Furthermore, these data regarding comorbidity need to be implemented in daily practice: every specialist and general practitioner treating allergic patients should consider the possibility of comorbidity, ask patients to complaints about each possible affected organ and treat them accordingly. Finally, allergy affects almost one third of the people living in a western society and it can affect a patients life, professionally, socially and privately, in a major way. Although many people still consider allergy to be a minor ailment, the results of this study show that allergy has a major impact in every day life. Further attention to the quality of life in this patient group is therefore not a luxury but a necessity.

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