Development of new treatment modalities for atopic dermatitis
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Chapter 12

SUMMARY AND CONCLUSIONS

Atopic dermatitis (also known as atopic eczema), a common skin disorder characterised by itching, is becoming more and more prevalent. Atopy refers to a group of hypersensitivity phenomena. The atopic diseases—asthma, hay fever, hives and atopic dermatitis—are what can appear in a person who has an atopic predisposition or atopic syndrome. While there are many different names for this particular form of dermatitis around the world—in the Netherlands it is most often called *atopisch eczeem* or *constitutioneel eczeem*—we use the most common ‘international’ name in this dissertation, i.e. ‘Atopic Dermatitis’, in part because atopic is more meaningful (i.e. more specific) than ‘constitutional’. Dermatitis is a skin disease accompanied by itching, redness, swelling, blisters, scratch marks, etc. There are various different kinds of dermatitis, depending on the cause and the location in which it appears, but the most common form is atopic dermatitis.

It is estimated that one out of five Dutch people have had the disease at some point in their lives and that around 400,000 patients are currently suffering from it in the Netherlands. Atopic dermatitis has a major impact not only on the patient's own quality of life, but also on his or her family or household. Besides being unpleasant, the disease also involves considerable costs in both money and time: treating a moderate-to-serious case of dermatitis requires an average of two to three hours each day.

The treatment usually consists of standard ointments or creams (emollients) along with a corticosteroid ointment or fatty cream, which was developed back in the early 1950s. Surprisingly, no better treatments have become available since then. Those that have been developed more recently are hardly ever used since they are too impractical, involve high costs or have serious side effects.

The lack of effective new therapies is even more remarkable considering that safer and more effective medicines have been found for most other diseases, precisely in the past half century. We were naturally very excited when a new class of medicines was found in the 1990s that might provide an alternative for the use of corticosteroid ointments and creams.
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The first chapter of this dissertation offers an overview of the current treatments for atopic dermatitis. These comprise general advice, indifferent therapies, antibacterial therapies, diets, recommended topical therapies, systemic therapies, photo(chemo)therapy, hospitalisation, clinics, the treatment of complications, alternative and experimental therapies (including discussions of the medicines described in chapters 3 through 9). Moreover, the epidemiology, etiology, clinical symptoms and course of the disease, the diagnosis and the differential diagnosis are likewise discussed. The second part of Chapter 1 looks at the various different phases in the development of new medicines and the set-up/objective of the studies discussed in chapters 2 through 10.

In studying treatments for atopic dermatitis, it is of the utmost importance that the patients involved in fact have real atopic dermatitis rather than some other form of dermatitis or even a different skin disorder altogether. While this would seem an obvious condition, it can be a real problem in practice: in the case of two different patients who were convinced that they had atopic dermatitis and who wanted to take part in the studies mentioned in Chapter 4 and Chapter 6, respectively, we ultimately determined the diagnosis of psoriasis vulgaris.

In Chapter 2, the diagnosis of atopic dermatitis is described in more detail on the basis of contemporary ideas about the disease. A standard test for determining whether or not someone has atopic dermatitis has yet to be developed. The diagnosis is usually made on the basis of clinical phenomena (i.e. what it looks like and where it is located) and anamnesis. Generally accepted criteria are usually used for studies on new treatments. On the basis of the current understanding of the disease, we were able to adjust the most commonly used criteria for atopic dermatitis (Hanifin & Rajika 1980), especially the most important feature of the atopic syndrome: the tendency to produce allergen-specific IgE. In our opinion, the presence of these antibodies is a crucial feature of the diagnosis of atopic dermatitis, and we have therefore included it as a required symptom in the 'Millennium Criteria for the Diagnosis of Atopic Dermatitis'. These new criteria can help ensure that the studies are conducted exclusively with patients who have an 'irrefutable' case of atopic dermatitis, so that the specific efficacy of the new treatments against atopic dermatitis will become more clear.

Studies on the maturation of white blood cells in patients with atopic dermatitis have shown that a certain type of white blood cell (T-helper cells) are more apt to mature into so-called Th 2 cells in atopic patients. These Th 2 cells make substances (chemokines) that cause reactions in the body that we can ultimately
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observe as dermatitis. Medicines such as ciclosporine, which work as inhibitors for these cells, turn out to be very effective against atopic dermatitis. Unfortunately, ciclosporine has serious side effects—especially in the long term. In an attempt to prevent these side effects, especially to the kidneys, the application of ciclosporine in the form of an ointment was tested. This proved to be ineffective, however. In the 1990s, new substances were discovered that inhibit the T cells in the same way as ciclosporine. In contrast to the latter, the new substances are able to pass through the skin and can thus potentially be applied as an ointment or cream. One of these new medicines is pimecrolimus, which was selected for its suppressive properties from among hundreds of variants of the substance ascomycine. As no name had yet been given to this particular ascomycine derivative when these first studies were being conducted, the abbreviation SDZ ASM 981 was used. In the meantime, the name pimecrolimus has been assigned to the substance, which will be marketed under the registered name Elidel.

Chapter 3 is a report on the first study ever conducted on pimecrolimus cream (Elidel®, SDZ ASM 981) as a medicine against atopic dermatitis. Together with tacrolimus (Protopic®, FK506), discussed in chapters 8 and 9, this medicine forms a new class of corticosteroid-free medicines: the topical immunomodulators. The study, in which we treated two dermatitis (test) sites per patient (one with pimecrolimus cream and one with a standard cream), consisted of two components. In the first part, both creams were used twice a day. In the second part, another 20 (new) patients were treated, but only once a day. While it is very common to prescribe the use of ointments and creams twice a day, this is not always necessary. Some medicines, like corticosteroid ointments and creams, are virtually just as effective when used only once a day. Moreover, there is considerably less chance of side effects occurring when the usage is reduced to once a day. The study with pimecrolimus cream showed that using the cream twice a day would improve the symptoms of dermatitis by 71.9%, while there was a 37.7% improvement when it was used only once a day. The improvement noted in the patients’ symptoms already on their first visit following the start of the treatment (after just two days of use) was a very good sign indeed. For a skin disease like atopic dermatitis, in which itching is the primary feature, it is crucial that a therapy begin to work quickly.
Once the efficacy of pimecrolimus was demonstrated, and once it turned out that the cream had to be used twice a day after all, a study was conducted to investigate the required strength of the cream. The results of this research, which involved 260 patients in 14 European hospitals, are described in Chapter 4. The maximum technically feasible strength/amount (1%) was compared to strengths of 0.6%, 0.2%, 0.05% and 0%. At the same time, the effect of these creams was compared to an 'old-fashioned' potent corticosteroid cream (betametason). The results showed us that the new cream once again proved effective even when used by hundreds of patients from various different countries and that the pimecrolimus cream with the highest concentration worked the best. After three weeks of use, however, the potent corticosteroid cream turned out to work better than the most effective pimecrolimus cream.

Topical medicines will only work if they are able to penetrate the skin. The drawback of this is that the medicines thus absorbed may have side effects elsewhere in the body. We know for example that using ciclosporine—a medicine that works according to the same mechanism as pimecrolimus—can produce serious side effects. It is therefore of great importance that a new medicine such as pimecrolimus not only be capable of penetrating the skin, but also that it remain in the body in such low concentrations that it will not cause any serious side effects. We investigated this in the study described in Chapter 5. The amount of pimecrolimus that the skin absorbs and that enters into the bloodstream is minute: it concerns millionths of grams (ng). This makes conducting a study like the one described in chapters 5 and 6 extremely difficult. A millionth of a gram of pimecrolimus more or less would already interfere with our measurements, so we had to do our utmost to prevent the blood samples from becoming 'polluted'. To this end, the patients were admitted to the hospital, given special (sterile) gowns at regular intervals, were not allowed to leave their rooms or to apply the medicine to their skin themselves, were taken to separate rooms where special nurses took samples of their blood, etc. These precautionary measures later proved to have been justified: in one instance, a blood sample was taken incorrectly, and the resulting measurement was 5-10 times higher than the other 443 blood samples. 78% of the samples contained so little pimecrolimus, if any, that it could no longer be detected in laboratory tests.
Once it had become clear that the amount of pimecrolimus remaining in the body after three weeks of using pimecrolimus cream was so very minute, the question was raised as to whether even those small amounts might not accumulate over long-term use and thus eventually cause side effects after all. Moreover, a medicine meant to be used over a long period of time needed to be tested over a long period. To this end, we developed the study discussed in Chapter 6. In developing this study, we assumed that patients with an average-to-serious case of dermatitis could be treated successfully with pimecrolimus cream alone (as a mono-therapy). The results of the study from Chapter 4 were as yet unknown to us at that time. In order to be able to continue the research after 6 months with a minimum of 15 patients, we asked 20 patients to take part. While no one had dropped out before term in the previous studies, we thought it would be a good idea, considering the length of the study (12 months in total), to ask an additional five patients. Unfortunately, a large number of the participants did stop after a few months, as their serious cases of dermatitis could no longer be kept under control with pimecrolimus cream alone. In order to be able to complete the study successfully in spite of this, we doubled the number of participating patients. In addition, potent corticosteroid ointments were used more often for shorter periods (maximum 14 days in total) in the event of exacerbations of the dermatitis that did not improve with pimecrolimus cream alone. Besides these new insights about an effective use of the new medicine, the study showed us that pimecrolimus did not accumulate in the body, even after months of use. Indeed, the opposite proved to be the case: traces of the new medicine could only be found in the blood during the first months of the use of the new cream. The more the skin healed, the less of the new medicine it absorbed. It therefore appears that it would be impossible to apply too much pimecrolimus cream. In this study—in which the pimecrolimus cream was applied in a way that more closely resembled how normal patients would use a cream (thus no longer in a special wing of the hospital as in the study in the previous chapter, but simply by rubbing it on themselves at home)—the amount of medicine in the blood was considerably lower: 98% of the 918 blood samples contained too little (if any) medicine to be observed in the laboratory (LoQ=0.5ng). This was also the first study in which pimecrolimus cream was applied for a longer period (a maximum of 12 months). The favourable effect continued, whereas the corticosteroid ointments normally used quickly show a habituation effect (tachyphylaxy).
We investigated another one of the hundreds of derivatives of ascomycine, SDZ ASD 732, in the study described in Chapter 7. The difference between this substance and pimecrolimus, from the earlier studies, is that SDZ ASD 732 has no effect on the T cells and mastcells in laboratory research (in vitro), while both medicines had proven effective as a treatment for contact-allergic dermatitis in experiments with animals. The set-up of our study of SDZ ASD 732 was identical to that of the proof-of-concept study with pimecrolimus cream. Unfortunately, the results were disappointing in this case. It is possible that a suppressive effect on the T cells (and mastcells) is a crucial factor for the effectiveness of this new class of medicines and that an animal model with contact dermatitis is not a suitable model for the treatment of humans with atopic dermatitis.

Chapters 8 and 9 deal with tacrolimus, which people have known about longer than pimecrolimus. Tacrolimus is a product from a fungus found on a mountain northeast of Tokyo. The anti-bacterial effect was found to be disappointing, although the substance did have a strong effect on the immune system, and on the T cells in particular. For some years now, tacrolimus has therefore been administered both intravenously and in capsules as an immunosuppressive drug after organ transplants. During the research, tacrolimus tablets turned out to be very effective against skin diseases in which T cells play a major role (psoriasis, atopic dermatitis). Unfortunately, when tacrolimus capsules are used against skin diseases, they have the same side effects as ciclosporine tablets. In contrast to the latter, however, tacrolimus does work as an ointment.

The research described in Chapter 8 deals with the effect of a lengthy treatment with tacrolimus ointment. 316 patients in thirty hospitals in eleven European countries participated in the study: 200 patients for a period of six months and 116 patients for twelve months. They treated all their dermatitis sites twice a day with tacrolimus ointment with a strength of 0.1%. This strength was chosen because it had demonstrated the least side effects in earlier research. The effectiveness of the various strengths of ointment was investigated once again in a subsequent study. The primary goal of the research was to study the safety of the new medicine; to a lesser extent, its effect was also considered. The most common side effects were a burning sensation (47%), itching (24%) and redness of skin (12%). While itching and redness are also symptoms of dermatitis, the burning sensation was clearly a side effect but one that fortunately passed quickly. This side effect was often reported, especially in the first days of the use of tacrolimus ointment. There was little absorption of the medicine via the skin, and the concentration of the medicine in the blood (as a
measure for the systemic exposition) was minor. In 76% of the patients, the concentration was lower than 1 ng/ml. The effect of the ointment was good to excellent for 54%, 81% and 86% of the patients after one week, six months and 12 months, respectively.

Once the efficacy and safety of tacrolimus ointment had been demonstrated for adult patients, the first study involving the use of tacrolimus ointment on children could begin. The results of this research are described in Chapter 9. In this international study, 560 children were divided into three groups. 189 of these pediatric patients were treated with 0.03% tacrolimus ointment, 186 of them with 0.1% tacrolimus ointment, and the remaining 185 with a standard corticosteroid ointment (1% hydrocortisone acetate ointment). After three weeks of using the ointments twice a day, the extent of the improvement in the dermatitis was greatest in the group with 0.1% tacrolimus ointment and least in the group with 1% hydrocortisone acetate ointment. With children, too, a passing period of a burning sensation on the skin after using the cream was the only side effect that appeared more often in the groups of children who were treated with tacrolimus ointment, compared to those who were treated with corticosteroid ointment.

Chapter 10 describes a study involving an entirely different kind of medicine, namely cipamfylline, a powerful inhibitor of phosphodiesterase. It is known that the leukocytes of atopic dermatitis patients have abnormally high cyclic AMP phosphodiesterase activity. This high activity could be inhibited in laboratory research (in vitro) with phosphodiesterase inhibitors. Cipamfylline is a potent and selective inhibitor of phosphodiesterase-4. To investigate both the effectiveness and safety of this new medicine as a treatment for atopic dermatitis, we compared the effect of 0.15% cipamfylline cream with that of both a placebo cream and a standard treatment for atopic dermatitis (hydrocortison-17-butyrate). After two weeks of using the creams twice a day, the cipamfylline cream appeared to work significantly better than the placebo cream. But the effect of the corticosteroid cream (hydrocortison-17-butyrate) was significantly better in reducing the dermatitis, as expressed in the 'Total Severity Score', which was calculated using the various different symptoms of dermatitis as evaluated by the researchers on a scale of one to four. While a difference could be demonstrated statistically, we were not impressed by the clinical improvement of the dermatitis sites that the participants treated. The negligible clinical effect led us to refrain from participating in subsequent studies with cipamfylline cream.
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The final chapter, Chapter 11, describes the results of a study with ultraviolet therapy. It is already well known that sunlight, and in particular ultraviolet rays, have a favourable effect on the course of atopic dermatitis. Different parts of the ultraviolet spectrum are used for the treatment of patients: UVA, UVB, combinations of UVA and UVB or combinations of UVA with psoralens (i.e. photochemotherapy). Research has shown that an acute exacerbation of atopic dermatitis is best be treated with as much UVA as possible. The disadvantage of high doses UVA is that it easily burns the skin, however. This burning is caused by part of the spectrum of UVA rays (wavelengths up to 330 nm). By designing equipment that would only emit UVA radiation that does not cause burning (340-400 nm), high dosages could easily be administered. This became possible with the advent of UVA-1 therapy. The first thirteen patients we treated for atopic dermatitis with UVA-1 therapy in our centre were followed intensively. The results of their treatment are described in Chapter 11.

Since it is not uncommon that, besides the desired rays, radiation outside the intended spectrum is also emitted, we started with low amounts as a precaution. These were doubled on a daily basis for five days until we had reached the maximum dosage. In hindsight, the effect of the unintended radiation turned out to be quite minimal, and we now advise beginning immediately with high dosages. The effect of the lower doses in the first week was even a slight worsening of the dermatitis, possibly as a result of having stopped treatments that had been effective. The participants were treated five (working) days each week, for three weeks. Following the therapy, the clinical score (SCORAD) decreased by 50%. One week after treatment (follow-up), the improvement was still 47%. We conclude that UVA-1 therapy is an effective treatment for patients with serious atopic dermatitis. This therapy is hard on the patients due to the length and the frequency of the treatments. On the other hand, it produces few side-effects, and there is no rebound effect afterwards: after stopping with the treatment, the participants showed no direct exacerbation. The effect of the treatment can be improved by starting immediately with high doses.
Summary

In this dissertation, a number of new treatment modalities are discussed for the treatment of atopic dermatitis. Of these, the application of pimecrolimus, tacrolimus ointment and UVA-1 therapy are the most promising. UVA-1 therapy is already available. In the Netherlands, however, there are very few hospitals that have the facilities for this treatment. Hopefully, our research with the relatively inexpensive (medium-dosage) equipment will contribute to the introduction of this therapy in more locations. Much more—and more lengthy—research will be required for the medicinal treatment of atopic dermatitis. Fortunately, the numerous studies involving tacrolimus ointment and pimecrolimus cream are currently at such an advanced stage that the introduction of these two new treatments can be expected in the Netherlands in the near future. The fact that atopic dermatitis is especially prevalent among children makes it only logical that these new medicines have also been well tested for use with children. The topical immunomodulators will be one of the first treatment modalities that will already have been tested extensively for use with children before their introduction.

Unfortunately, a curative therapy still unavailable. As the human genome is further unravelled, it is expected that more and more will become clear about the predisposition for the atopic syndrome. This could well lead to a ‘golden standard’ test for the diagnosis of atopic dermatitis and to more specific therapeutic and preventive interventions.