Development of new treatment modalities for atopic dermatitis
van Leent, E.J.M.

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Chapter 1B

Introduction to development of new treatment modalities and aims of the studies
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INTRODUCTION

This thesis is about the development of new therapeutic modalities for atopic eczema. In order to develop new therapies it is important to have a good overview of the etiology, pathogenesis, course and current treatments available for this disease (chapter 1A). Since a well defined diagnosis is the basis for the development of new therapies, chapter 2 will discuss recently developed new criteria for the diagnosis of atopic dermatitis. This introduction reviews and illustrates the way in which new drugs become available on the market. This thesis concentrates on the development of SDZ ASM 981 (1) (pimecrolimus, Elidel®), FK506 (2) (tacrolimus, Protopic®), cipamfylline (3), and UVA-1 therapy (4-5).

Different treatment modalities
The performance of various clinical studies according to regulations is a prerequisite before introducing a new treatment (6). The demands for these studies may vary in different countries depending on the modality involved and the local law and regulations. For instance concerning the modality there are less regulations and laws for introduction of non-drug treatments like ultraviolet radiation than for introduction of new oral drug entities. Safety data concerning new electrical devices are needed for UV-cabins, but information on exact UVA dosing, side-effects, indications, precise description of the treatment, contraindications, interactions are not regulated but left to the profession. UVA-1 therapy in atopic dermatitis, made possible by recently developed fluorescent bulbs, is described in chapter 11 and forms an example of development of a new therapeutic entity by the profession itself.

Studies with new drugs
For drug treatment many laws and detailed regulations are available. These regulations also deal with the setup of the clinical studies. For this reason the development of new drugs is divided into several phases.

Phase 1
First safety and toxicology data have to be obtained in cell culture systems and animals. After studies in small animals (mice, rats) studies in larger animals (dogs, pigs) are performed. Conclusions of animal studies are extrapolated to human volunteers and patients. As soon as safety data of animal studies are available, safety studies in humans can start. Usually healthy volunteers are subject of interest for these studies. Side effects, toxicology and other safety items are studied. Unfortunately there are no good animal models for skin therapies nor for itch or atopic dermatitis (7). Therefore in special occasions
healthy volunteers might be replaced by patients (sometimes also called phase 1-2 studies). This is shown in chapters 5 and 6. Because the skin of healthy volunteers may not absorb the drug under investigation (SDZ ASM 981), a study with atopic dermatitis patients was performed. Practical issues such as cooling or other special storing conditions of the drug can be resolved after the end of stability (phase 1) studies.

Phase 2
Phase 2 studies are performed in patients. Efficacy and safety are studied. These studies should start after a certain range of phase 1 studies are finished, but to gain time the phase 2 studies start usually before the end of phase 1 studies. This explains why in the initial phase 2 studies the exposure (in time and extent) to the drug is limited, because long term phase 1 studies are still ongoing. As soon as long term phase 1 studies have been successfully completed, the phase 2 studies can be longer and with a higher exposure to the developed drug. In phase 2 studies efficacy and safety are studied in a limited number of patients. By treating patients on only one arm while not treating the other they can be considered as patient and control at the same time. In this way the number of participating patients can be limited. This was done in the first clinical study with SDZ ASM 981 cream (chapter 3). Dose finding is usually also subject of phase 2 studies. Not only the optimal concentration of the drug needs to be studied, but also the frequency of application. Unfortunately application schemes for the use of new drugs are not always studied in an early phase 2 study. Sometimes they are not performed at all, or just before launching to the market. Another item often not studied is the risk for contact sensitization and photo (contact) sensitization. After phase 1 sensitization studies in healthy volunteers, the sensitization studies should be repeated in phase 2 studies with patients, especially when the risk for sensitization is somewhat higher in the patients who will use the drug in the future (e.g. atopic dermatitis)(8-9).

Phase 3
The phase 3 studies are large multi-center trials to study the efficacy and safety of the drug in large groups of patients during a longer time to confirm the results of phase 2 studies. Because of the large numbers of patients and investigators involved, these studies are exceptionally expensive(10) and complex. Comprehensive preparations are necessary. First a protocol must be developed by a team of investigators (for instance: statisticians, pharmacologists, research physicians and the pharmaceutical company involved). When a protocol is written only by investigators without experience in the performance of clinical studies and by people who don't know the patients nor the illness, the study probably will be unsuccessful. For this reason
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we participated in the development of all the protocols of the studies in this thesis, especially where it concerned practical issues. Several meetings were organized with the other members of the research teams to discuss the protocol outline or the draft protocols. After the protocol is developed a case report form (CRF) has to be designed. This is an often underestimated, essential part of a study. All the investigators have to understand the way in which data should be collected. Especially CRF's used for multi-center studies must be designed using the input of the investigators with experience in performing clinical studies, the patients and the scoring systems. In order to collect the optimal data, all investigators have to be instructed and/or trained. For this reason investigator's meetings are organized. During these meetings it appears that although the scoring systems for atopic dermatitis (SCORAD (11-13) chapter 3, EASI (14) chapters 4, 8, and 9) seem easy, the inter-observer variation is large. For example: before the first multi-center study with SDZ ASM 981 (Chapter 3) all investigators were instructed by us during three meetings, decreasing the inter-observer variation in particular for the extent of the disease (body surface area, BSA).

Phase 4

Long term safety studies after a new drug is on the market (post-marketing studies) can be very useful, but these studies are often used as a marketing tool for the introduction of new drugs (seeding trials)(15). Phase 1, 2 and 3 studies are obligatory for the registration of a new drug by the authorities, but there are less regulations for phase 4 studies. FK506 and SDZ ASM 981 successfully passed the phase 1, 2 and 3 studies and phase 4 studies will start in the near future (16).

Selection of investigators

Before the start of a study, investigators have to be selected. Some pharmaceutical companies select study centers based on their experience in previous studies. Lists of top ranking investigators and top ranking countries for clinical studies are kept. For phase 1-2 studies the best performing centers are selected, for the selection of centers to be involved in later studies (phase 3-4) also marketing purposes will be important. As principal investigator in early (phase 1-2) studies, we participated in and co-organized several investigator meetings for upcoming large phase 3 and phase 4 studies. Our experience with a new drug in a clinical setting was very helpful for new participating investigators. Also during the performance of a multi-center study, we, as the principal investigator were a 'mentor' for the local participating centers. This late effect of participating in phase 1-2 studies is one of the reasons to
participate in these studies, even though these studies have disappointing results (for instance chapter 7).

**Performing studies**

Not only practical advice for other local centers must be provided, also in your own center advice and training is needed. To have a consistency in the assessments, new trial-nurses and physicians have to be trained in particular during long term studies. Patients have to be looked after and motivated to continue the sometimes very unpractical treatment or visit schedules (chapters 3 and 5). Interim analyses can be done for different purposes. They can be very helpful to correct ongoing studies (as done in chapter 6) or even to stop unsuccessful studies (chapter 7). Participants and investigators should always be blinded till the end of the study.

**Studies in children**

Most patients with atopic dermatitis are children under 10 years of age (17). The illness usually starts at the age of 3 months and serious exacerbations may occur (18). So, a new treatment for atopic dermatitis must be suitable for (very young) children (19). When a therapy is relatively contra-indicated for children, such as ultraviolet therapy (20-21) or systemic immunosuppressive treatment (22-25), it can only be used in a limited number of patients. After studies with animals, healthy volunteers and adult patients, studies in children are performed. In chapter 9 we present the results of a multi-center study with FK506 (26) in children. A multi-center study with SDZ ASM 981 (27) in children (28) is still ongoing.

Studies in children are different from studies in adult patients (29). Important differences are: children do not choose their treatment, they do not treat themselves and do not report the outcome of the treatment themselves. So clinical studies in children, such as the study in chapter 9, have their own ethical problems (informed consent by parents), practical problems (restricted amount of blood that may be withdrawn), and other outcome measurements (parents instead of patient assessment of clinical symptoms).

**Results of studies**

Results of well designed studies should be published. This is endorsed by many scientific medical journals. In fact however, journals are in particular interested in successful studies. For instance chapter 3 was accepted for publication easily while an identical study with another but unsuccessful compound (chapter 7) was not easily accepted. After completion of the study report or publication of the data in a scientific medical journal the participating patients and the local
ethical committees have to be informed about the outcome of the study, in a proper way.

The costs of new drugs
The mean amount of money needed for a successful new drug is hundreds of millions US dollars (10). Most governments are not able or willing to spend such an amount of money on the development of new drugs (30). One of the main expensive tasks of pharmaceutical companies is the development of new drugs, but, to please their investors they have to make profits. As a result of this, new drugs are mainly developed for illnesses that are relatively frequent and for patients who are able to pay for the new products. Atopic dermatitis is one of the most common skin diseases, and the incidence of the disease is increasingly high, especially in western countries (31-32). It is therefore surprising that since the invention of the topical corticosteroids in the early fifties (33) no major new drug has become available for the treatment of atopic dermatitis patients (34-35).

AIMS OF THE STUDIES

After the development of topical corticosteroids fifty years ago (33) no new treatments for the common disease atopic dermatitis, with still increasing incidence (36), have become available. Although topical steroids are effective in atopic dermatitis, the use may be limited by the side effects or by the sometimes inadequate fear of patients or their parents for corticosteroids (corticophobia (37)). This results in inappropriate treated children with atopic dermatitis, and therefore non-steroid therapies are desperately needed.

The primary aim of this thesis was the development of new treatment modalities in all its steps:

- small, short-term and early studies (needed to study the safety of the new treatments)
- large multi-center studies (late in drug development)
- studies in adults
- studies in children (because most patients with atopic dermatitis are young children).

To perform successful studies in atopic dermatitis, the disease studied has to be well defined. The secondary aim of the studies in this thesis was to implement new insights in the immunopathogenesis (38) of the disease in the diagnostic criteria. This results in the Millennium Criteria for Atopic Dermatitis. We expect that these more strict criteria may lead to unambiguous results of clinical studies.
REFERENCES


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Introduction to drug development
