General discussion and summary

This thesis describes a series of studies on erythroderma. In **chapter 1** the aims of the study are presented followed by **chapter 2** which provides a short review of the literature about erythroderma. In **chapters 3, 4 and 5** basic epidemiological aspects and in **chapters 6 and 7** immunological aspects are discussed. Finally in **chapter 8** a work-up protocol for patients with erythroderma is presented.

Basic epidemiological aspects of erythroderma

Erythroderma is a striking but uncommon clinical entity in the practice of most dermatologists. Data on the incidence of erythroderma are scarce and limited to a rough estimate in one study demonstrating an annual incidence between 1-2 patients per 100.000 inhabitants [1]. By performing a survey among 78% of dermatologists in the Netherlands we found a slightly lower incidence of 0.9 per 100.000 inhabitants (**chapter 3**). Because we recruited data from the majority of dermatologists working in the Netherlands, we believe that our data are more representative than those of Hasan et al, since they used data from only one clinic [1]. The difference between these data seems minimal, but one may not forget that when dealing with such a small incidence numbers the difference between 1 and 2 is substantial.

Our survey showed also that the majority of patients with erythroderma in the Netherlands are diagnosed and treated in non-academic centers (**chapter 3**). Only more complicated cases with diagnostic dilemmas and therapy resistance are referred to academic centers. As expected, we were able to show that the causes of erythroderma are different in an unselected dermatological population compared to a selected population at university hospitals. Not surprisingly, exacerbation of a preexisting dermatosis, such as eczema and psoriasis, was the most frequent cause of erythroderma among the patients diagnosed at non-academic hospitals, 61% compared with 50% at the university hospitals. On the contrary, idiopathic erythroderma and cutaneous T-cell lymphoma were less frequent diagnosed in non-academic setting.

With our study we have been able to show that when dealing with questions regarding incidence and cause of erythroderma an investigation among all dermatologists is mandatory in order to get reliable results, because the majority of patients with erythroderma is diagnosed and treated by non-academic dermatologists.

Reports on the prognosis of patients with erythroderma are conflicting. In general, patients with malignant erythroderma such as Sézary syndrome are known to have a bad prognosis with a mean survival rate between 2,5 to 5 years [2;3], but studies on survival among patients with benign erythroderma have never been performed. In our series of 102 patients with erythroderma (**chapter 4**) the mortality in the whole group was 43% which is high in comparison to other studies in which it has

been between 11-64% [4-8]. This high mortality rate in our study is explained by the long follow-up period and also by the relatively high prevalence of malignant lymphoma in our group. When only the survival among patients with benign erythroderma was investigated, estimated survival of men with "benign erythroderma" was significantly lower than in an age-matched control group of the general population. In women it was lower but not statistically significant. The difference in survival between patients in our group and in the general population is difficult to explain. A possible explanation is that, most patients were treated with topical corticosteroids and sometimes systemic prednisone. It is known that corticosteroids can induce atherosclerosis, and as a consequence, an increase in cardiovascular deaths [9]. In our group most of the patients or 12 out of 29 (41%) died because of cardiovascular diseases (**chapter 4**). We did not investigate whether this is more or less than in the general population.

In most patients with erythroderma the cause can be established, but a proportion remains undetermined (idiopathic erythroderma). The relative frequency of idiopathic erythroderma has been reported between 9-46% in different series [1;4-8;10-14]. During follow-up, a proportion of these patients has developed cutaneous T-cell lymphoma (CTCL) [7;8;13]. Two of our patients (7%), both with chronic persistent idiopathic erythroderma for many years, progressed into cutaneous T-cell lymphoma (**chapter 5**). This is less than has been reported in other series where it was around 20% [7;8;13]. A possible explanation for this difference is that few of our patients had chronic persistent idiopathic erythroderma, but these patients are more likely to develop cutaneous T-cell lymphoma than patients with less chronic disease [7;13]. Based on our results we conclude that only patients with chronic persistent idiopathic erythroderma, which is a minority of the cases, have an increased risk of developing cutaneous T-cell lymphoma and therefore need a close and long-term follow-up. In these patients we recommend, at least annually, analysis for circulating Sézary cells and/or CD4/CD8 ratio of blood lymphocytes and histopathological investigation of skin (**chapter 8**).

Pathogenesis of erythroderma

Erythroderma may have different causes, but at present it is unclear whether the underlying patho-mechanisms that lead to erythroderma are identical or different depending on the original disease [15;16]. As a consequence of cutaneous inflammation, erythroderma may be considered to be secondary to a complicated interaction of cytokines and cellular adhesion molecules. Therefore, we performed studies on cytokine- and adhesion molecule expression in the skin of patients with different types of erythroderma and compared this with the expression in non-erythrodermic diseases.

Data are available on cytokine mRNA expression in skin of patients with Sézary syndrome, but not on other types of erythroderma. These studies demonstrate a Th2 cytokine profile in Sézary syndrome [17-21]. In accordance with the above-mentioned studies, also at the protein level, we found

predominantly IL-4 in the dermis of patients with Sézary syndrome. IFN-γ was also present, albeit in a lesser number of cells (**chapter 6**).

In contrast to Sézary syndrome, in all benign reactive erythrodermas studied (namely idiopathic erythroderma, erythrodermic atopic dermatitis and miscellaneous group), cells in the dermal infiltrate were mainly IFN-γ positive. There was no significant difference in IL-4/IFN-γ ratio between groups (**chapter 6**).

Data regarding the local cytokine pattern in mycosis fungoides are partly conflicting [18;22-24]. Most studies have shown a Th1 cytokine profile and some studies have suggested a shift from Th1 to Th2 profile in advanced stages of mycosis fungoides [18;22;23]. In the present study of patients with mycosis fungoides an equal number of cells in the dermal infiltrate were expressing IL-4 and IFN-γ (median IL-4/IFN-γ ratio =1). The IL-4/IFN-γ ratio in mycosis fungoides was significantly lower than in Sézary syndrome (**chapter 6**). This further supports the earlier data on cytokine expression in Sézary syndrome and mycosis fungoides showing a change in the cytokine profile towards Th2 in Sézary syndrome [18;21].

No data were available on adhesion molecule expression on endothelial cells *in situ* in erythroderma, however some data on circulating adhesion molecules have been published [25]. In the present study we demonstrate a high and persistent expression of VCAM-1, ICAM-1, E-selectin and P-selectin on endothelial cells in patients with erythroderma (**chapter 7**). However, there was no significant difference in expression of adhesion molecules between Sézary syndrome and benign reactive erythroderma. There was neither statistical difference in adhesion molecule expression between Sézary syndrome and mycosis fungoides, nor could we find a significant difference in adhesion molecule expression between erythrodermic atopic dermatitis and lesional skin of atopic dermatitis except for VCAM-1.

According to this we can postulate that the cytokine- and adhesion molecule expression in the skin in benign reactive erythroderma is as monomorphous as the clinical picture showing upregulation of adhesion molecules on endothelium and infiltration of inflammatory cells mainly expressing Th1 cytokine profile. This is not different from any other, more localized, chronic inflammation of the skin such as non-erythrodermic atopic dermatitis, psoriasis and lichen ruber planus [23;26-29]. On the other hand, in malignant erythroderma, such as in Sézary syndrome, the skin infiltrate is mainly expressing Th2 cytokine profile.

These studies on cytokine- and adhesion molecule expression indicate that at least in benign reactive erythrodermas, a similar patho-mechanism or final common patho-mechanism may be involved, resulting in the relative uniform clinical picture of erythroderma. The skin diseases, which can progress into erythroderma such as atopic dermatitis, psoriasis and lichen ruber planus, even though they all have a different types of inflammation probably induced by a different pathogenetic

mechanisms, are all expressing Th1 cytokine profile in lesional skin [23;26-29]. As we know, in inflammation in general, there are factors, which initiate and maintain the inflammation but there are also factors, which suppress it, otherwise the inflammation would not terminate. We can only speculate on that, but in patients which develop erythroderma this suppressor mechanisms, probably on a cellular level, seems to be failing resulting in total cutaneous failure and erythroderma. In Sézary syndrome a different patho-mechanism seems to be involved. In these patients malignant T-cells expressing Th2 cytokine profile are in dynamic equilibrium between the skin and vascular compartments [2;19;20;30;31]. Infiltration and proliferation of these T-cells in skin subsequently cause widespread inflammation resulting in erythroderma.

Work-up protocol for patients with erythroderma

Even though erythroderma is a rare disease one must realize that in the Netherlands about 150 new patients are diagnosed annually. By advocating a work-up protocol for these patients we believe that it will be easier for the dermatologist to manage these patients (**chapter 8**). On the one hand it will limit unnecessary investigations on some patients but on the other hand, when actually needed, further investigations will be correctly performed. This protocol is based on simple investigations, which can be performed in nearly all hospitals in the Netherlands. This is of utmost importance because as we have shown most of the patients with erythroderma are diagnosed and treated in non-academic settings.

It is our hope that by presenting this work-up protocol the quality of care for patients with erythroderma will be enhanced and even fewer patients with erythroderma will be referred to university hospitals.

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