Innovative therapies and new targets in psoriasis

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REDUCTION OF DIFFERENT INFLAMMATORY CELL TYPES OF THE INNATE IMMUNE SYSTEM IN PSORIATIC SKIN DURING ETANERCEPT TREATMENT

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ABSTRACT

To investigate whether specific markers for innate immunity would diminish with successful treatment in psoriasis, we analyzed lesional and non-lesional skin biopsies taken from patients with moderate to severe psoriasis during 12 weeks of treatment with etanercept in correlation with the clinical response. In the clinical responders (PASI reduction > 50%), all markers (CD3, CD68, CD161, elastase, BDCA-2, TNF-α) showed a decline during treatment, indicating a pivotal role for innate immunity in the pathogenesis of psoriasis.
BACKGROUND AND QUESTION ADDRESSED

Over the years, various hypotheses on psoriasis pathogenesis have been proposed, varying from keratinocyte-centered, to T-cell mediated, to aggravation at the level of innate immunity. The latter is based on the remarkable improvements seen in clinical trials with tumor necrosis factor (TNF-α) antagonists, together with the discovery of activation of several cellular elements and humoral components of the innate immune system in lesional and non-lesional psoriatic skin.

We hypothesized that, if malfunctioning of the innate immune system is somehow a pivotal initiator of psoriasis, successful treatment of psoriasis would diminish the expression of markers of innate immunity.

EXPERIMENTAL DESIGN

We analyzed lesional and non-lesional skin biopsies, taken on baseline, weeks 3 and 12, from 6 patients with moderate to severe psoriasis treated with etanercept (a humanized TNF-α receptor) 50 mg subcutaneous twice weekly for 3 months. This investigation was a biopsy substudy of the study registered at www.clinicaltrials.gov under NCT00195507. The Psoriasis Area and Severity Index (PASI) and the Body Surface Area (BSA) were assessed at baseline, weeks 3 and 12. Skin biopsies were immunohistochemically stained for CD3 (T cells), CD68 (macrophages), CD161 (NK-T cells), elastase (neutrophils), BDCA-2 (plasmocytoid dendritic cells) and TNF-α. All sections were randomly coded and were analyzed through manual quantification of the twenty high power fields per section. Manual quantification was done by two independent observers blinded for order, patient and clinical data. The epidermal and dermal regions were separately counted. Positive staining of CD3, CD68, CD161, BDCA-2, elastase and TNF-α was expressed as positive cells/mm².

RESULTS AND CONCLUSIONS

In the lesional skin biopsies of the clinical responders (Table 1, n=3, PASI reduction > 50%), all investigated markers were clearly reduced after 12 weeks of treatment with etanercept (Figure 1A), whereas no reduction of these markers was seen in the non-responders (Figure 1B). Particulary CD68, CD161, elastase and BDCA2-positive cells declined early during treatment (Figure 2).

Early reduction of CD68-positive cells was also seen by Gottlieb et al. during etanercept treatment, by Marble et al. during adalimumab treatment and by Markham et al. during infliximab treatment.

A rapid decline of CD161-positive cells during etanercept treatment was also described by Van Lingen et al. CD161 is a marker for NK-T cells. Activation of NK-T
Table 1 Demographics and clinical response

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<td>13.6</td>
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PASI, Psoriasis Area and Severity Index; BSA, Body Surface Area; na, data not available

Cells results in prompt release of high levels of cytokines like INF-γ and TNF-α, and NK-T cells have mutual interaction with dendritic cells and keratinocytes, which are thought to be relevant in psoriasis. Remarkably, Bovenschen et al. described a case in which immuno-histochemical analyses in a non-responsive patient on infliximab showed a correlation between the number of epidermal NK-T cells and the lack of clinical efficacy, supposing a pathogenic role for these cells in psoriasis 22.

When looking at elastase-positive cells in clinical responders during etanercept, our results are corresponding with Gottlieb et al.18. Vincek et al. reported a rapid decline of neutrophils in lesional skin already one day after an infusion with infliximab 23.

No previous investigations are present on the response of plasmacytoid dendritic cells in psoriatic skin during etanercept treatment. During adalimumab treatment a similar fast response was noted by Marble et al.19 BDCA-2-positive cells are mostly plasmacytoid dendritic cells, which are present in normal-appearing skin of psoriasis patients, but in contrast, absent in normal skin of healthy individuals 24.

Our results show a clear decline in CD3-positive cells at week 12, which is in line with Mahiques et al. 25. According to Gottlieb et al. and Zaba et al. this decrease of T cells can be appreciated at a much earlier time point during etanercept treatment 18,26. Previous studies done with infliximab all showed a rapid decline of CD3-positive cells in lesional skin 20,23,27,28.

To our surprise we did not find a clear effect of TNF-α inhibitor etanercept on the TNF-α expression in the skin in situ in responders. Studies with another TNF-α inhibitor, infliximab, did show a decline in TNF alpha-positive cells 20,23,29. These contradictory results could be due to the marker used to detect TNF-α. TNF-α is a
Figure 1 Effects on cell numbers in lesional and non-lesional epidermis and dermis over time in responders (A) and non-responders (B, next page) during treatment with etanercept. Data are shown as means with SD. L, lesional; NL, non-lesional.
Figure 1 Effects on cell numbers in lesional and non-lesional epidermis and dermis over time in responders (A, previous page) and non-responders (B) during treatment with etanercept. Data are shown as means with SD. L, lesional; NL, non-lesional.
cytokine produced by many different cell types and different immunohistochemical markers will demonstrate TNF-α in various different ways, as shown by Van der Laan et al. 30. Furthermore, it has been described that levels of TNF-α in the circulation are stable or even increase after etanercept treatment, probably due to an increased stability of etanercept-bound TNF-α 31. Moreover, immunohistochemistry gives no information about the biological activity of the detected TNF-α.

Information on the effect of etanercept treatment on the different leukocyte subsets in lesional and non-lesional psoriatic skin and possible relationship to the clinical response is very limited. Gottlieb et al. showed after one month of treatment a rapid and complete reduction of IL-1 and IL-8 (immediate/early genes), followed by progressive reductions in many other inflammation-related genes, and finally somewhat slower reductions in infiltrating myeloid cells (CD11c+ cells) and T lymphocytes 18. Zaba et al. observed reduction of inflammatory dendritic cell products that drive Th17 cell proliferation (IL-23), as well as Th17 cell products and downstream effector molecules (IL-17, IL-22, CC chemokine ligand 20, β-defensin 4) 26.

Mahiques et al. showed a significant decrease of CD4+ and CD8+ T cells after 12 weeks of treatment in the epidermis and dermis of psoriatic skin 25, whereas Van Lingen et al. only showed a significant decrease of CD8+ T cells in the dermis after 12 weeks in responders 21, as well as a significant decrease of CD161 in the dermis of responders.

Figure 2  Immunohistochemical staining of psoriatic skin in a responding patient before and after treatment with etanercept. CD68-positive cells at baseline (a) and week 12 (b). BDCA-2-positive cells at baseline (c) and week 12 (d).
In addition to the earlier studies describing the immunohistochemical effects of treatment with etanercept in psoriasis, this is the first study in which CD68+ cells and BDCA-2+ cells were investigated. Our data are in concordance with previous similar studies and show that several innate immunity markers diminish during effective treatment with etanercept, indicating that innate immunity might play a role in the pathogenesis of psoriasis. Further investigation is needed to understand the involvement of other cell types and cytokines of innate immunity.

**REFERENCE LIST**

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