Alitretinoin abrogates innate inflammation in palmoplantar pustular psoriasis

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Summary

Background Palmoplantar pustular psoriasis is often recalcitrant to therapy. Here we evaluated the therapeutic effect of alitretinoin in patients with recalcitrant palmoplantar pustular psoriasis and investigated subsequent immunopathological alterations.

Methods Seven patients with palmoplantar pustular psoriasis were treated with oral alitretinoin 30 mg once daily for 12 weeks. Efficacy was assessed by palmoplantar pustular psoriasis area and severity index (PPPASI), visual analogue scales (VAS) on intensity of pain and pruritus and an overall patient assessment. Immunohistochemical staining for neutrophil elastase, CD3, CD4, CD8, CD1a, CD11c, CD303, CD68, CD69, CD208 and HLA-DR was on lesional skin biopsies obtained before and after 12 weeks of treatment.

Results PPPASI and VAS for pruritus and pain decreased significantly after 12 weeks of treatment with alitretinoin. The overall patient assessment ranged from 60% to 90% clinical improvement. In correlation with clinical improvement a significant reduction, particularly of neutrophils, macrophages and dendritic cells, was also observed in the skin sections. Alitretinoin was well tolerated except for headache during the first month of treatment in two patients. Limitations of the study are a missing control group and the concomitant usage of topical therapy.

Discussion Our findings suggest that alitretinoin may represent a new and promising therapy for recalcitrant palmo-plantar psoriasis and warrants further controlled studies to confirm efficacy and safety of alitretinoin in this disease.
were obtained from lesional skin before beginning therapy and from skin adjacent to the first biopsy at week 12 from six patients. Prior to the second biopsy no topical treatment except for emollients was used for 2 weeks. Biopsy specimens were routinely processed for histology (Hematoxylin & Eosin staining) as well as for immunohistochemistry, using the streptavidin biotin complex/alkaline phosphatase method as described previously. 4,5 The following primary antibodies were used: neutrophil elastase (clone: NP57; DakoCytomation, Glostrup, Denmark), CD3 (clone: F2-38; DakoCytomation), CD4 (clone: 4B12; Novocastra, Newcastle-upon-Tyne, UK), CD8 (clone: C8/144B; DakoCytomation), CD1a (clone: O10; DakoCytomation), CD11c (clone: 5D11; Novocastra), CD303/BDCA2 (clone: 108H10:03; Dendritics, Lyon, France), CD208/LAMP3 (clone: 104.G4; Dendritics), CD68 (clone: PG-M1; DakoCytomation), CD69 (clone: CH11; Abcam, Cambridge, UK) and HLA-DR (clone: TAL.1B5; DakoCytomation). Quantitative analysis was performed by using the digital image analysis system NIS-Elements Software BR 2.30 (Nikon, Tokyo, Japan), as previously described. 5 Statistical analysis was

![Graph](image_url)

**Fig 1.** (a) PPPASI and (b) VAS values for pruritus and (c) pain in palmoplantar pustular psoriasis before and after 12 weeks of treatment with alitretinoin 30 mg once daily. Horizontal black lines indicate mean values. (d) Photographs demonstrating marked improvement of palmoplantar pustular psoriasis and plaque psoriasis before alitretinoin (A, D, G), after 8 weeks (B, E, H) and 12 weeks (C, F, I) of treatment with alitretinoin 30 mg once daily in two patients.
performed using the Wilcoxon signed-rank test. P-values <0.05 and 0.01 considered statistically significant, were and highly significant, respectively.

**Results**

**Clinical assessments**

As shown in Figure 1a, the PPPASI score decreased significantly (P = 0.01) after treatment with alitretinoin 30 mg once daily. The mean PPPASI score before and after treatment was 17.5 (±SD: 3.6) and 4.3 (±SD: 2.1), respectively. A 50% improvement in the PPPASI score (PPPASI 50) was achieved by 100% of patients at week 12. Four of seven patients (57%) reached PPPASI 75. A significant decrease of the VAS values for pruritus (P = 0.01) and pain (P = 0.01) was also observed (Fig. 1). The mean VAS values before and after treatment were 7.2 (±SD: 1.6) and 1.5 (±SD: 0.9) for pruritus and 6 (±SD: 1.4) and 1.1 (±SD: 1.2) for pain, respectively. The overall patient assessment ranged from 60% to 90% clinical improvement. Notably, three of four patients who had an unsatisfactory response to acitretin reached PPPASI 75.

Representative photographs before and after 3 months of treatment from two patients are shown in Figure 1b. In tendency, pustules appeared to resolve quicker than erythema and desquamation. Interestingly, practically complete resolution of the plaque psoriasis lesions on the extremities was also seen in all three patients with concomitant plaque psoriasis. All patients reported practically complete discontinuation of concomitant topical therapy with steroids, vitamin-D analogues or calcineurin-inhibitors during the first 8 weeks and were using moisturizers thereafter.

Therapy with alitretinoin was well tolerated except for headache during the first month of treatment in two patients, which has previously been observed in 20% of all patients.3 Laboratory assessments were unremarkable in all patients.
treatment with alitretinoin. This is in agreement with previous studies reporting an increase of LC in psoriatic lesions after treatment with acitretin\textsuperscript{14} or TNF-antagonists.\textsuperscript{6} Cumberbatch et al.\textsuperscript{15} described the mobilization of LCs and their migration to draining lymph nodes after intradermal injection of tumor necrosis factor alpha or interleukin-1 beta. The marked reduction of activated dendritic cells and macrophages, which are known to be a major source of TNF-\(\alpha\), may therefore partly also explain the increase of epidermal LCs found in this study. In addition, it has been recently described that LCs are precommitted to immune tolerance induction,\textsuperscript{16} thus their increased numbers might actually play a role in disease control. Regarding T cells it has been found that alitretinoin mainly results in polarization change but not apoptosis of T cells. 9-cis retinoic acid actually inhibits activation-driven apoptosis of T cells.\textsuperscript{17} Such mechanisms might explain the relevant remaining numbers of T cells after treatment with alitretinoin.

Our study is limited by a missing control group and the concomitant usage of topical therapy. In addition, data on the duration of disease control by alitretinoin both during active treatment and after stopping intake are still lacking. A placebo-controlled double-blind study is planned to investigate these questions.

In conclusion, the presented data suggest that alitretinoin may represent a promising therapy for recalcitrant palmoplantar pustular psoriasis.

What's already known about this topic?

- Alitretinoin provides an efficacious treatment for chronic eczema and exerts immunomodulatory and anti-inflammatory activity.
- However, the therapeutic effects of alitretinoin in patients with recalcitrant palmoplantar pustular psoriasis are still unknown.

What does this study add?

- Alitretinoin may lead to rapid resolution of palmoplantar pustular and plaque psoriasis.
- Alitretinoin abrogates inflammation by reducing the number of neutrophils, myeloid and plasmacytoid dendritic cells and macrophages, as well as partly of T-cells.

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References


10 Zapata-Gonzalez F, Rueda F, Petriz J et al. 9-cis-Retinoic acid (9cRA), a retinoid X receptor (RXR) ligand, exerts immunosuppressive effects on dendritic cells by RXR-dependent activation: inhibition of peroxisome proliferator-activated receptor gamma blockers some of the 9cRA activities, and precludes them to mature phenotype development. J Immunol 2007; 178:6130–9.


