BJD
British Journal of Dermatology

Alitretinoin abrogates innate inflammation in palmoplantar pustular psoriasis

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Accepted for publication
14 May 2012

Conflict of interest
N. Yawalkar has served as a consultant to Basilea.

DOI 10.1111/j.1365-2133.2012.11063.x

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.

Palmoplantar pustular psoriasis (PPP) is a chronic inflammatory skin disease which is often resistant to treatment.[1,2] Oral alitretinoin (9-*cis* retinoic acid) is a vitamin A derivative with immunomodulatory and anti-inflammatory activity that has emerged as a novel treatment for recalcitrant chronic hand eczema.[3] The precise mechanisms of action of alitretinoin resulting in reduction of skin inflammation are still poorly understood. Here we evaluated the therapeutic effect of alitretinoin and investigated alterations in the inflammatory cell infiltrate in patients with recalcitrant PPP.

Patients, material and methods

Seven patients (six female, one male, aged 22–75 years) were referred to our department for further treatment of recalcitrant PPP. Previous treatments included topical steroids (n = 7), vitamin D derivates (n = 7), calcineurin inhibitors (n = 2), tar (n = 7), phototherapy (n = 5), acitretin (n = 4) and methotrexate (n = 2). The mean duration of disease was 11·2 years (range 1–31 years). Three patients had concomitant plaque psoriasis. Four patients had a history of active cigarette-smoking. After obtaining their informed written consent all patients were treated with oral alitretinoin 30 mg once daily for 3 months. Patients were allowed to continue topical steroids (clobetasol propionate or betamethasone dipropionate cream twice weekly) and vitamin-D analogues (calcipotriene or tacalcitol ointment up to 2–3 times weekly), or calcineurin-inhibitors (tacrolimus 0·1% ointment up to 2–3 times weekly) during the initial 6–8 weeks and encouraged to only use moisturizers thereafter. Efficacy was assessed with palmoplantar pustular psoriasis area and severity index (PPPASI), the intensity of pain and pruritus determined by a visual analogue scale (VAS; 0–10) and an overall patient assessment (0–100% improvement). Laboratory tests included assessment of liver enzymes, blood lipids and thyroid hormones before and during therapy.

With approval by the Medical Ethics Committee of the Canton of Berne, Switzerland, five-mm punch biopsy specimens

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), CD 303/BDCA2 (clone: 108H10·03; Dendritics, Lyon, France), CD208/LAMP3 (clone: 104.G4; Dendritics), CD68 (clone: PG-M1; DakoCytomation), CD69 (clone: CH11; Abcam, Cambrige, 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

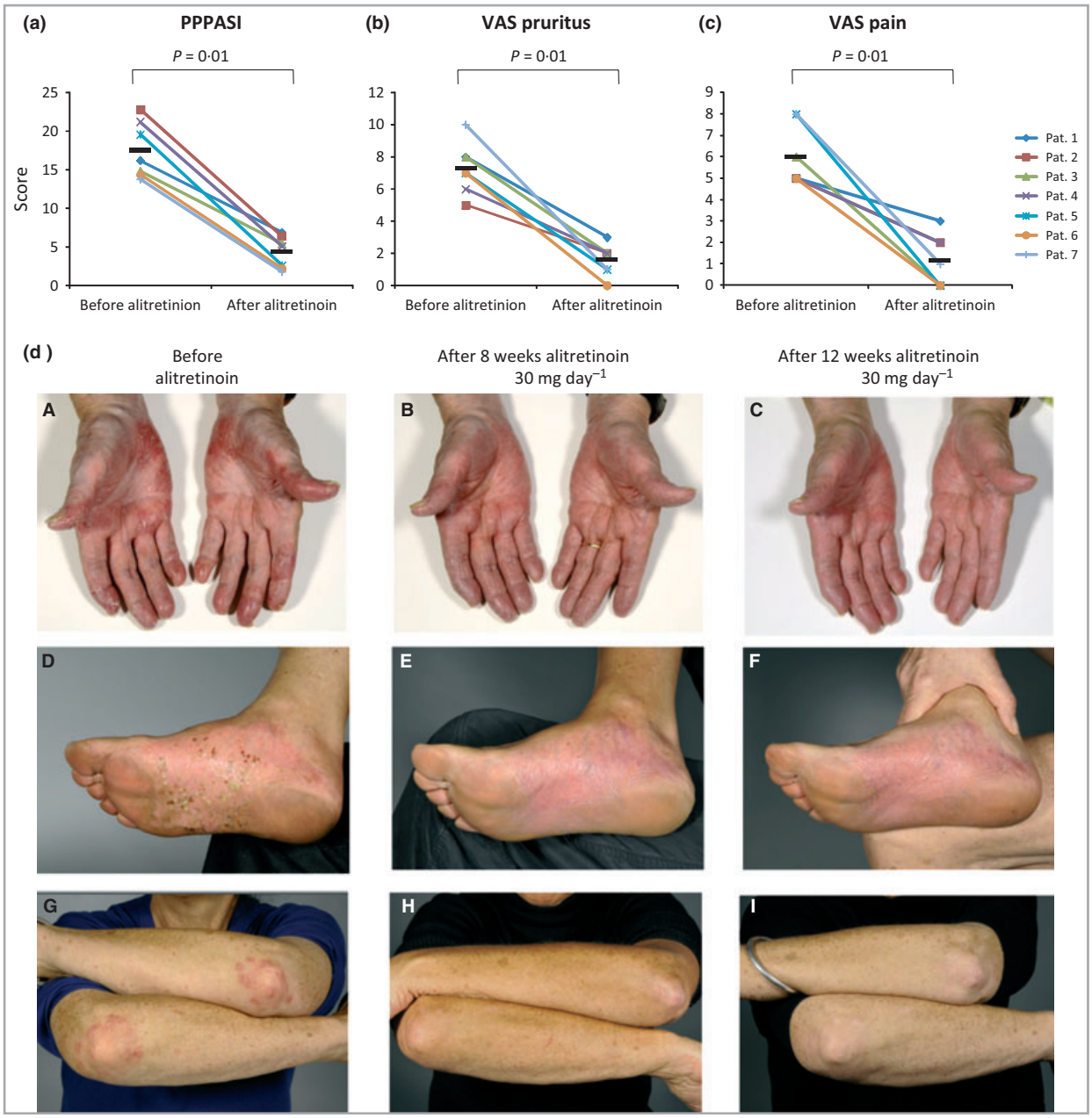

Fig 1. (a) PPPASI and (b) VAS values for pruritus and (c) pain in palmoplantar pustular psoriasis before and after 12 weeks of treatment with alitretinoin 30 mg once daily. Horizontal black lines indicate mean values. (d) Photographs demonstrating marked improvement of palmoplantar pustular psoriasis and plaque psoriasis before alitretinoin (A, D, G), after 8 (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.

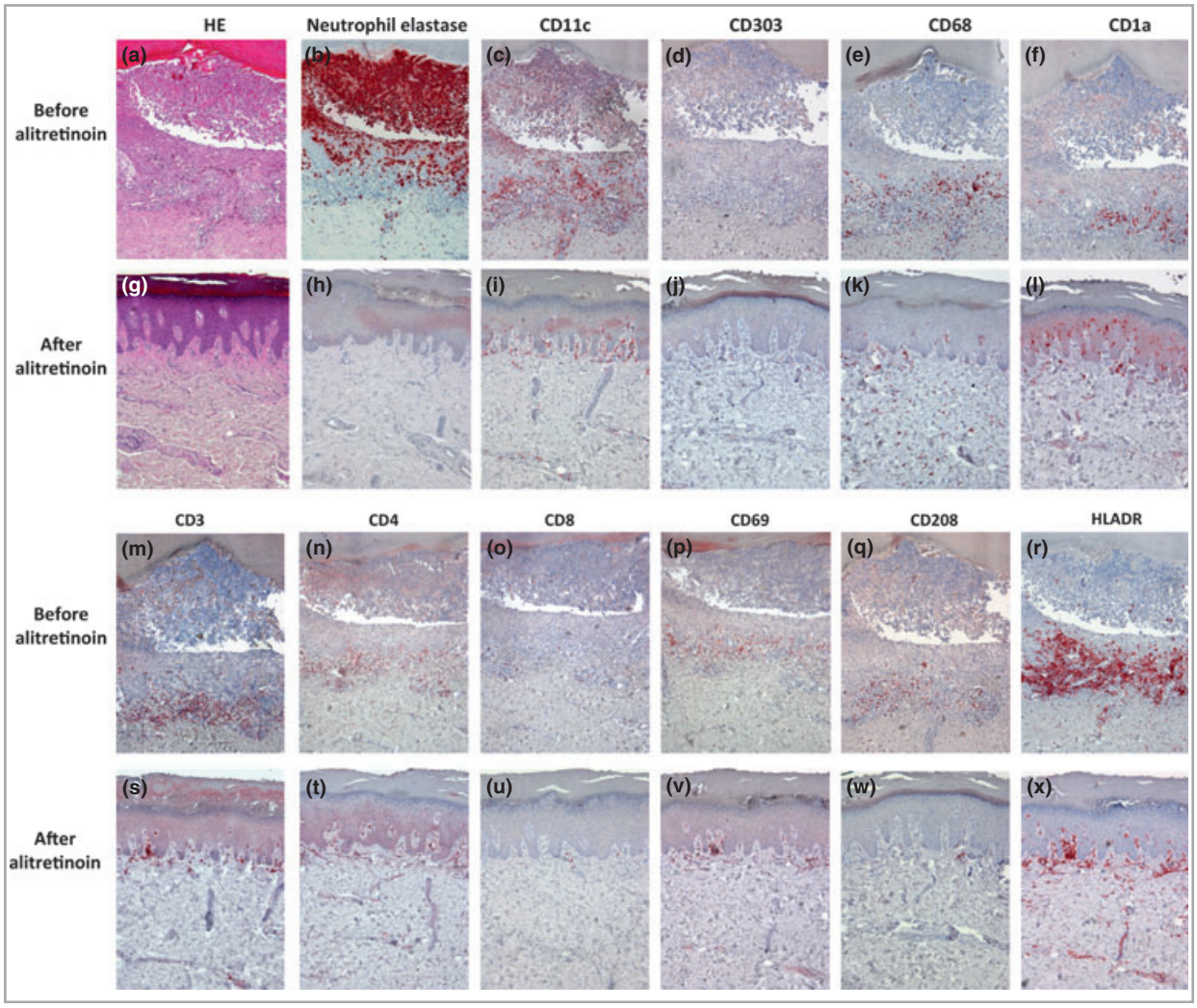

Fig 2. Representative histological (HE staining) and immunohistochemical findings of different leukocyte populations showing a significant reduction of the proinflammatory infiltrate from one patient before treatment (a–f, m–r) with alitretinoin and at week 12 (g–l, s–f). Original magnification ×100.

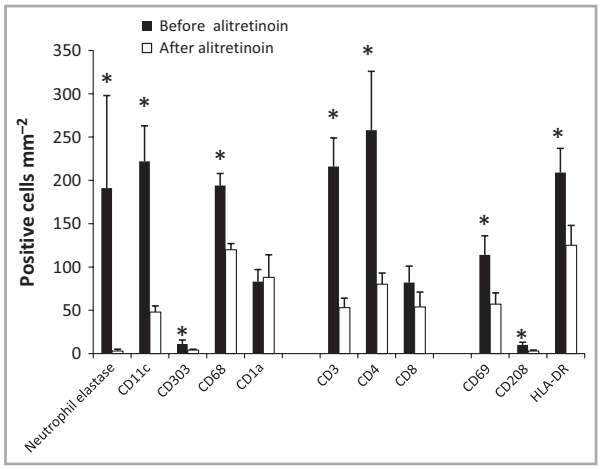

Fig 3. Quantification of the inflammatory cells before and after treatment with alitretinoin 30 mg once daily (n = 6). Mean values ±SD are indicated. * $P > 0{\cdot}05$.

Immunohistopathologic findings

In correlation with clinical improvement a marked reduction of the inflammatory infiltrate was observed in all patients. Representative stainings from one patient and quantification of the inflammatory cells are shown in Figures 2 and 3, respectively. In particular, a significant ($P < 0{\cdot}05$) decrease of neutrophils (neutrophil elastase), myeloid (CD11c) and plasmacytoid (CD303) dendritic cells as well as macrophages (CD68) was observed. Although CD3+ and CD4+ T cells also decreased significantly, relevant remaining numbers of CD8+ T cells were still detected after treatment. Before treatment, both T cells (CD69, HLA-DR) and dendritic cells (CD208, HLA-DR) had an activated phenotype. The expression of these activation markers was significantly decreased after 12 weeks of treatment with alitretinoin. Interestingly, a slight increase in the number of CD1a+ Langerhans cells (LC) was observed.

Discussion

This study provides evidence of improvement of PPP in seven patients treated with alitretinoin 30 mg once daily for 12 weeks. In addition, patients were able to almost completely discontinue concomitant topical therapy with steroids, vitamin-D analogues or calcineurin-inhibitors within the first 8 weeks. Furthermore, clinical improvement was paralleled in all patients by a marked reduction of the innate and partly of the adaptive cellular infiltrate.

Alitretinoin has been reported to exert immunomodulatory properties by affecting various cell types including keratinocytes,[7,8] fibroblasts,[9] mast cells,[10] dendritic cells[11] and T cells.[12] Furthermore, by suppressing the expression of chemokine receptors, it was suggested to inhibit the recruitment of inflammatory cells.[13] Our immunohistochemistry results showed a marked decrease especially of neutrophils, myeloid and plasmacytoid dendritic cells and macrophages. In contrast, a slight increase in number of CD1a-positive LC was observed after treatment with alitretinoin. This is in agreement with previous studies reporting an increase of LC in psoriatic lesions after treatment with acitretin[14] or TNF-antagonists.[6] Cumberbatch *et al.*[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-α, may therefore partly also explain the increase of epidermal LCs found in this study. In addition, it has been recently described that LCs are precomitted to immune tolerance induction,[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.[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 tretment 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.

Acknowledgment

We thank Basilea for providing alitretinoin. We are indebted to U. Laederach, who provided excellent technical support.

References

1 Mrowietz U, van de Kerkhof PC. Management of palmoplantar pustulosis: do we need to change? *Br J Dermatol* 2011; **164**:942–6.
2 Chalmers R, Hollis S, Leonardi-Bee J *et al.* Interventions for chronic palmoplantar pustulosis. *Cochrane Library* 2009; **4**:1–49.

3 Ruzicka T, Lynde CW, Jemec GB *et al.* Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; **158**:808–17.
4 Hassan AS, Kaelin U, Braathen LR, Yawalkar N. Clinical and immunopathologic findings during treatment of recalcitrant atopic eczema with efalizumab. *J Am Acad Dermatol* 2007; **56**:217–21.
5 Schlapbach C, Ochsenbein A, Kaelin U *et al.* High numbers of DC-SIGN+ dendritic cells in lesional skin of cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2010; **62**:995–1004.
6 Gibbs S, Backendorf C, Ponec M. Regulation of keratinocyte proliferation and differentiation by all-trans-retinoic acid, 9-cis-retinoic acid and 1,25-dihydroxy vitamin D3. *Arch Dermatol Res* 1996; **288**:729–38.
7 Sørensen S, Sølvsten H, Politi Y, Kragballe K. Effects of vitamin D3 on keratinocyte proliferation and differentiation in vitro: modulation by ligands for retinoic acid and retinoid X receptors. *Skin Pharmacol* 1997; **10**:144–52.
8 Xiao R, Kanekura T, Yoshida N *et al.* 9-Cis-retinoic acid exhibits antifibrotic activity via the induction of cyclooxygenase-2 expression and prostaglandin E2 production in scleroderma fibroblasts. *Clin Exp Dermatol* 2008; **33**:484–90.
9 Ko J, Yun CY, Lee JS *et al.* Differential regulation of CC chemokine receptors by 9-cis retinoic acid in the human mast cell line, HMC-1. *Life Sci* 2006; **79**:1293–300.
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 blocks some of the 9cRA activities, and precludes them to mature phenotype development. *J Immunol* 2007; **178**:6130–9.
11 Dawson HD, Collins G, Pyle R *et al.* Direct and indirect effects of retinoic acid on human Th2 cytokine and chemokine expression by human T lymphocytes. *BMC Immunol* 2006; **7**:27.
12 Villablanca EJ, Zhou D, Valentinis B *et al.* Selected natural and synthetic retinoids impair CCR7- and CXCR4-dependent cell migration in vitro and in vivo. *J Leukoc Biol* 2008; **84**:871–9.
13 Werner B, Bresch M, Brenner FM, Lima HC *et al.* Comparative study of histopathological and immunohistochemical findings in skin biopsies from patients with psoriasis before and after treatment with acitretin. *J Cutan Pathol* 2008; **35**:302–10.
14 Gordon KB, Bonish BK, Patel T *et al. Br J Dermatol* 2005; **153**:945–53.
15 Cumberbatch M, Bhushan M, Dearman RJ *et al.* IL-1beta-induced Langerhans' cell migration and TNF-alpha production in human skin: regulation by lactoferrin. *Clin Exp Immunol* 2003; **132**:352–9.
16 Shklovskaya E, O'Sullivan BJ, Ng LG *et al.* Langerhans cells are precommitted to immune tolerance induction. *Proc Natl Acad Sci USA* 2011; **108**:18049–54.
17 Yang Y, Merćep M, Ware CF, Ashwell JD. Fas and activation-induced Fas ligand mediate apoptosis of T cell hybridomas: inhibition of Fas ligand expression by retinoic acid and glucocorticoids. *J Exp Med* 1995; **181**:1673–82.