QUANTITY, DISTRIBUTION AND IMMUNOPHENOTYPICAL MODIFICATION OF DENDRITIC CELLS UPON BIOLOGICAL TREATMENTS IN PSORIASIS

F. PRIGNANO, F. RICCERI, B. BIANCHI and T. LOTTI

Department of Dermatological Sciences, University of Florence, Florence, Italy

Received October 16, 2008 – Accepted February 25, 2009

Psoriasis is an immune-mediated disease which affects a large world population.

It has long been considered a dermatological disorder in which keratinocytes and lymphocytes play a relevant pathogenic role. The aim of our study is to more closely observe and better define the role of dendritic cells (DCs) in psoriasis. We made a comparative analysis of the antigenic profile and the number, by immunohistochemical and electron microscopical study, of skin biopsy samples from psoriatic patients before and 4 months after biological treatments. Our results demonstrate an abundant distribution of activated DCs in lesional skin of psoriatic plaques and a marked decrease after biological therapies [a decrease of 70% for Langerhans cells (LCs) and mature myeloid dendritic cells (mDCs) and of 50% for plasmocytoid dendritic cells (pDCs)]. Both previous reports and the results of the present study support an underlying persistent immune response involving DCs in the onset and persistence of psoriasis. As DCs play a pivotal role in pathogenesis of psoriasis by presenting antigens via major histocompatibility complex class (MHC) II molecules, the present study supports the view that biological therapies are also effective in clearing psoriatic lesions as well as in reducing the number of DCs.

Thirty years ago, Steinman and Cohon first described a novel cell type with dendritic morphology in the spleen (1). Since this observation, dendritic cells (DCs) have been identified circulating in blood and residing in many other tissues, including human skin.

DCs, as members of the Antigen-Presenting-Cell system (APC system), possess an extremely potent capability of stimulating resting T-cell (TC) proliferation and cytokine release and they play a crucial role in activating adaptive immune responses and immunomediated diseases.

Langerhans cells (LCs) are professional APCs needed for the activation of TCs responses, presenting both peptide and lipid antigens via Major Histocompatibility Complex Class II (MHC) and CD1a molecules on their surface, respectively. They are a subset of immature DCs that differentiate in the epidermis; for their specific location, LCs are the first immunologic barrier to pathogens. It is generally accepted that LCs encounter the antigens in the skin and then migrate to the draining lymph nodes via the dermal lymphatics, where the antigen is presented to TCs, thus initiating an immune response. By electron microscopy, LCs can be distinguished from other DCs by the presence of a typical cytoplasmic organelle, the Birbeck granule. By immunohistochemistry, LCs are characterized by the expression of Langerin/CD207, a type II transmembrane Ca2+-dependent lectin. The presence of Birbeck granules within LCs is dependent on the expression of the endocytic receptor Langerin (CD207), which is a C-type lectin

Key words: dendritic cells, psoriasis, biological therapies

Mailing address:
Prignano Francesca, MD
Department of Dermatological Sciences,
University of Florence, Villa Basilewsky,
via Lorenzo Il Magnifico n 104, 50129 Florence, Italy
Tel: ++39 0556264481 Fax: ++39 0556264499
e-mail: francesca.prignano@unifi.it

0394-6320 (2009)

highly expressed only at the LC surface. Langerin -/- mice lack Birbeck granules, but do not demonstrate defective immune responses, suggesting that the Langerin protein and Birbeck granules are not indispensable for immunity to skin pathogens (2). Moreover, disruption of the Langerin/CD207 gene abolishes Birbeck granules without a marked loss of LC function.

In recent decades, the predominant investigative pathway into immunopathogenesis of psoriasis vulgaris has been focused primarily on keratinocyte hyperproliferation (3), and secondarily on T lymphocyte alterations (4), with little or no consideration for the potential importance of DCs. The role of DCs as promoter of this disease, as well as of the recruitment of disease-specific TCs in the immunopathogenesis of psoriasis has recently gained more attention.

Recent observations, such as successful treatment with cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin (5), support the hypothesis that antigen-presenting dendritic cells could play a critical role in the pathogenesis of psoriasis and recent reviews on psoriasis have suggested a pathogenetic involvement of DCs (6-8).

In fact, DCs, due to their central position in the immune system as antigen presenting cells, may be a driver in the immune mechanism of psoriasis. Activation of DCs, production of cytokines (Interleukin IL-12, Interleukin IL-23) induced by DCs, antigen presentation to TCs by DCs and, subsequently, Th-1 cell activation with release of Tumour Necrosis Factor (TNF)-α and Interferon (IFN)-γ are all events playing a major role in the formation of chronic plaque psoriasis (9). Moreover, DCs are central players in the potentially self-sustaining type-1 inflammatory network and are viewed as the only cells able to work as an "immnunogenic bridge" between innate and acquired imunity (10).

Recent studies shave shown that DCs are increased in psoriatic skin and, overall, could equal or exceed the amount of TCs in old-standing lesions (11); moreover, their antigen-presenting activity is increased. Cutaneous DCs belong to different subsets: immature dendritic cells (iDCs), mature myeloid dendritic cells (mDCs, termed epidermal and dermal depending on their location), and plasmocytoid dendritic cells (pDCs). LCs, the most abundant subgroup of DCs in the skin, are identified by HLA Class II and CD1a expression.

All these DCs are increased in diseased skin.

In this study, we pointed to increased DCs and to DCs-TCs interaction as a crucial moment in the pathogenesis of psoriasis.

This study was designed to assess the presence, distribution and number of DCs in psoriatic skin before and after biological therapies (with both Anti-CD11a and Anti-TNF-α) to further characterize the role of DCs in psoriasis. In addition, it may contribute to clarifying the mechanisms of action of biological drugs in psoriasis.

MATERIALS AND METHODS

Study protocol

The aim of the present study is to show the presence, the antigenic profile and the ultrastructure of subsets of DCs in psoriatic patients before and after biological treatments, and to provide data on the role of these cell types in the pathogenesis of psoriasis.

Sixteen adult patients with chronic plaque-type psoriasis treated at the Department of Dermatological Sciences (University of Florence) were enrolled in the present study. The diagnosis of psoriasis was performed according to clinical features combined with the histopathological findings by a dermopathologist. Inclusion criteria were, at least Psoriasis Area and Severity Index (PASI) > 10%, failure/relapse with previous available treatments such as UVB-narrow band, methotrexate (Mtx), acitretin (Rtn), cyclosporine (CsA) and compatibility for a biological therapy. Six patients treated with anti-TNF-α (Etanercept –Enbrel, Wyeth Lederle S.P.A.- 50 mg twice a week) and ten with anti-CD11a (Efalizumab –Raptiva, Merck Serono S.P.A.- 1 mg/Kg/week). Eight of the subjects were male and eight were female; the range age was 24-64 years and the range duration of disease was 3-16 years (Table I).

Approval by the Medical Ethical Committee was obtained and all patients gave informed written consent.

Skin punch biopsies (6 mm) were obtained from a representive psoriatic lesion under local anesthesia with cloridrate mepivacaine. To analyze the influence of anti-psoriatic therapy on the presence of DCs, the biopsies were taken from the same patients before and after four months of biological therapy. Immunohistochemistry was performed with the antibodies listed in Table II. Moreover, an ultrastructural study was added.

Immunohistochemistry

Immunohistochemical staining using an alkaline phosphatase-anti-alkaline phosphatase (APAAP) method was performed to determine the expression of various DC subsets in psoriatic plaques before and after biological therapies (Raptiva *vs* Enbrel).

Mouse monoclonal anti-human antibodies (MoAbs) were used as primary reagents, as listed in Table II.

Biopsies were frozen at -80°C immediately following surgery; 6 μm cryostat serial sections were cut and immediately fixed with ice-cold acetone for 4 min, then subjected to staining. Thereafter, individual sections were incubated with the noted MoAbs for 60 min at room temperature. After washing in 0.01M phosphate-buffered saline (PBS), pH 7,4, for 10 min, the sections were incubated for 40 min with rabbit anti-mouse immunoglobulin antiserum (RAM; DakoCytomation, Glostrup, Denmark), and then processed with APAAP complex (Dako Cytomation). In order to enhance the labelling intensity, RAM/APAAP incubation was repeated twice. Binding of the complex was revealed by hexazotized new fuchsin as chromogenic substrate (Merk, Darmstadt, Germany). The sections were then counterstained with Mayer's haematoxylin. Control sections were incubated with normal mouse IgG.

All sections were examined using an optical microscopy (Diastar). Two investigators (FP and FR) read all tissue sections using an ocular micrometer with a rectangular area (0.125 x 0.25 mm^2) and the immunoreactive cells were counted in at least four randomly selected reticular dermal, papillar dermal and epidermal tissue areas. Discrepancies in the reading were resolved by a second parallel reading of the slides until consensus.

The reported histological score (presented in Table III) is the average of these observations. Each section was graded for labelling of epidermal, papillar and reticular dermal cells on a scale of 0-4, based on the number of immunolabeled cells for each antigen. Absence of immune-reactivity was scored as "0", more than 10 immunolabeled cells was scored as "4". We report the amount of immunostained cells in 4 scoring categories in order to match the level of positivity between readers.

Electron microscopy

DCs were fixed in a mixture of 2% formaldehyde and 2.5% glutaraldehyde in 0.1 mmol/l cacodylate buffer, pH 7.4 at 5°C for 3 h, followed by postfixation in 1% OsO_4 phosphate buffer, pH 7.4 at room temperature for 2 h. The specimens were dehydrated in a graded acetone series, passed through propylene-oxide and embedded in epon 812. Semithin sections were coloured with toluidine blue, while ultrathin sections were stained with uranyl acetate followed by bismuth nitrate or lead citrate, and examined with a JEM 1010 electron microscope (Jeol, Tokyo, Japan) at 80 kV.

Statistical analysis

Statistical analyses were carried out using SPSS program.

RESULTS

Immunophenotypic expression

To characterize the presence and the nature of DCs in lesional skin of psoriatic plaques, we stained

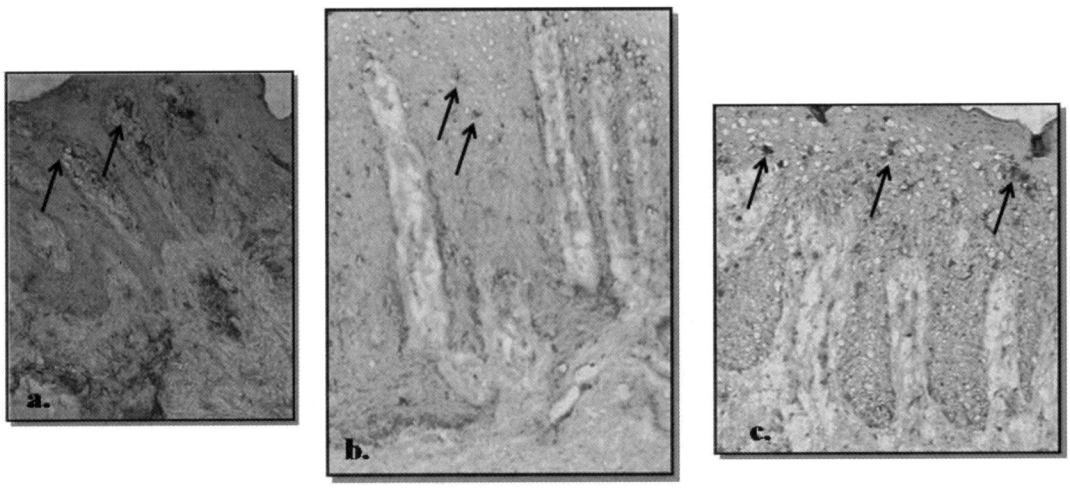

Fig. 1. *Langerin, a marker of differentiated Langerhans cells, is heterogeneously expressed. Langerin expression (arrows) in controls (**a**), upon treatment with Enbrel (**b**) and with Raptiva (**c**).*

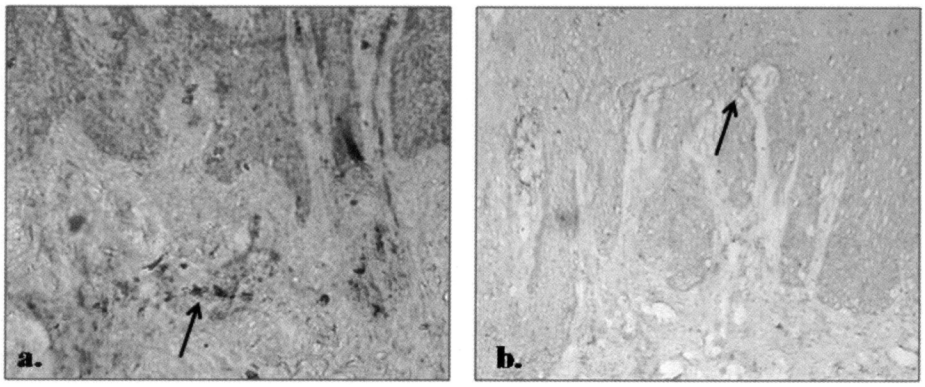

Fig 2. *CD83 is a monoclonal antibody able to stain mature DCs. Staining for CD83 (arrows) in controls (**a**) and upon treatment with Enbrel (**b**).*

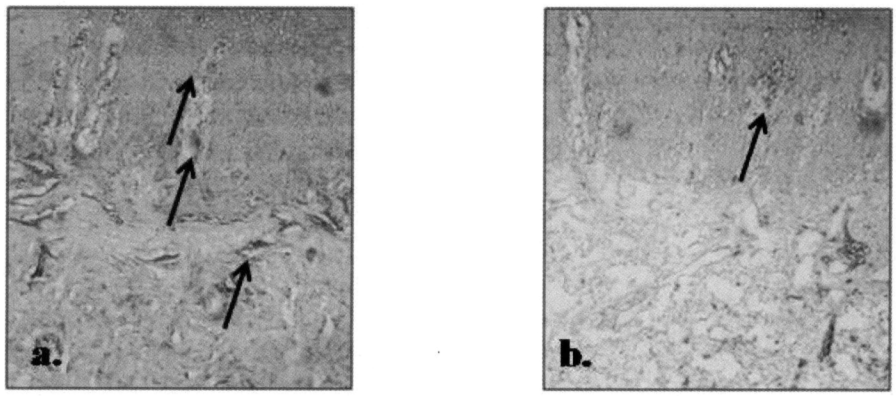

Fig. 3. *HLA-DR antigenic expression (arrows) upon treatment with Raptiva (a) and Enbrel (b). There is a clear-cut increase of HLA-DR positive DCs upon treatment with Raptiva.*

the samples with antibodies against several markers of DCs.

Within the DC population in skin biopsies of patients with psoriasis, LCs, CD1a+ Langerin+ are predominat (score 4) especially in the epidermis, in their most typical suprabasal position (score 4), but also in the papillar (score 3) and reticular derma (score 1). Typical dendritic processes were observed among keratinocytes, and in some areas they reached the superficial compartments of the epidermis. Their number was reduced after biological therapies (a decrease of 77%, 70% and 54% in epidermis, papillar and reticular dermis respectively). In patients undergoing Raptiva treatment the decrease was higher (90%, 86%, 79%) than in those treated with Enbrel (65%, 60%, 27%) (Fig. 1 a, b, c).

CD86 and CD83, the costimulatory and maturation molecules respectively, expressed on activated DCs were also immunostained; remarkable numbers of DCs in the lesional epidermis, and especially in papillar and reticular dermis, stained positive for these markers (score 2, 3 and 3 in epidermis, papillar and reticular dermis, respectively) (Fig. 2 a, b).

At variance with normal skin, which contains mainly LCs and dDCs, another DC distinct population has been identified in inflamed psoriatic skin, namely pDCs, which can be identified by the expression of BDCA-2. Of note, BDCA-2 immunoreactivity was detected in a few cells of lesional mid dermis (score 2) and papillary dermis (score 2). A significant decrease of this DC subset was detected after biological therapies: -12%, -

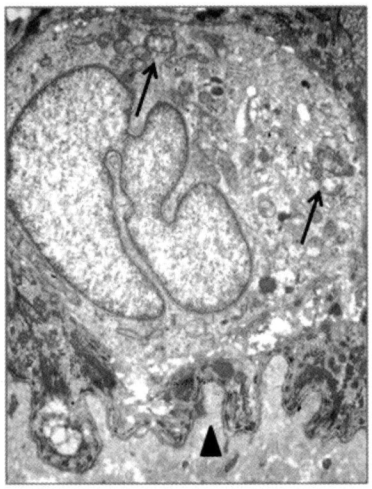

Fig. 4. *A Langerhans cell with a lobulated nucleus and many organelles – some of which are mitochondria (arrow) - in the cytoplasm. Most LCs are immediately on the basal membrane (arrow-head) (Magnification X7000).*

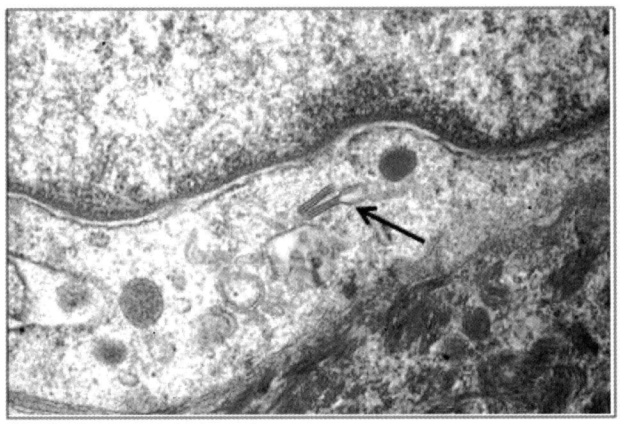

Fig. 5. *Detail of a LC, with some Birbeck granules within the cytoplasm, one with the typical racket-shaped morphology (arrow) (Magnification X15000).*

64% and -53% in epidermis, papillar and reticular dermis, respectively. Upon treatment with Raptiva the decrease was more prominent: -36%, -58% and -60%.

There was a massive infiltration of HLA-DR-positive cells in the lesional skin of psoriatic plaques, especially in the papillary dermis. HLA-DR staining, after biological treatment, revealed a completely different staining pattern in patients on Raptiva therapy versus patients on Enbrel therapy. In fact, HLA-DR+ DCs were more abundant in the patients treated with Anti-CD11a (score 3 vs score 2) than in those treated with anti-TNF-α (Fig. 3 a, b)

In summary, the presence of DCs in the epidermis and dermis in lesional psoriatic skin was diffused and very strong. In contrast, after biological therapies, the amounts in the epidermis and even more in the dermis was much weaker. The decrease after biological therapies was statistically significant for all DCs subsets.

Ultrastructure

By electron microscopy, two distinct DCs populations could be indentified: differentiated and poorly differentiated DCs.

Differentiated DCs were located in a suprabasal position and displayed clear-cut dendritic morphology (Fig. 4), with many processes extending among the keratinocytes. Most of them presented an indented nucleus, while few others showed a bi- or multi-lobulated nucleus. In their cytoplasms, these cells showed well-developed Golgi apparatus and rough endoplasmic reticulum, and many mitochondria. At higher magnification, in the Golgi area as well as in proximity to the plasma membrane, typical rod- or tennis racket-shaped Birbeck granules (Fig. 5: arrow) were visible. This description fits perfectly with classical LC morphology and suggests that these cells have attained full differentiation. The second population of DCs was represented by cells with smooth surface and less dendrites compared with the previous ones and showed round-shaped nuclei. The cytoplasm was much poorer in organelles and Birbeck granules were never detected.

DISCUSSION

Our data show that immature (CD1a+, Langerin+) and mature (CD83+, CD86+, DC-LAMP+) mDCs and pDCs (BDCA-2+) are increased in psoriatic lesional skin and that there is a statistically significant decrease in their number after biological therapies, with both anti-CD11a (Raptiva) and anti-TNFα (Etanercept), with minor differences

Table I. *A list of patients with their clinical information involved in this study.*

Patient	*Age*	*Sex*	*Year of duration*	*PASI score*	*Activity of psoriasis*	*Previous treatment*	*Actual treatment*
1)B.A.	41	F	3	19	Worsening	Rtn, CsA	Etanercept
2)A.B.	25	F	3	14	Worsening	UVB, CsA	Efalizumab
3)A.B.	60	M	20	17	Worsening	UVB, Rtn	Efalizumab
4)P.B.	45	M	13	14	Worsening	CsA, Mtx	Efalizumab
5)C.F.	37	F	7	20	Worsening	CsA, Rtn	Etanercept
6)F.F.	27	M	11	20	Worsening	Rtn, Mtx	Etanercept
7)G.F.	58	M	2	15	Worsening	CsA, Mtx	Etanercept
8)A.G.	55	M	17	20	Worsening	CsA, Rtn	Efalizumab
9)F.G.	28	F	7	12	Worsening	UVB, CsA	Etanercept
10)F.M.	48	M	15	20	Worsening	CsA, Mtx	Etanercept
11)A.N.	64	F	8	12	Worsening	UVB, CsA	Efalizumab
12)N.N.	40	M	15	13	Worsening	Rtn, CsA	Efalizumab
13)P.R.	65	F	4	12	Worsening	UVB, CsA	Efalizumab
14)C.T.	61	F	16	15	Worsening	CsA, Mtx	Etanercept
15)F.V.	58	M	3	11	Worsening	UVB, CsA	Etanercept
16)A.Z.	30	F	10	15	Worsening	CsA, Mtx	Efalizumab

Table II. *Primary monoclonal antibodies.*

Antibody	**Clone**	**Isotype**	**Code**	**Dilution**	**Source**
Langerin (CD207)	DCGM4	IgG1 mouse	IM3449	1:40	Immunotech
CD83	HB15e	IgG1,k mouse	550401	1:60	BD Pharmingen
CD86	IT2.2	IgG2a,K mouse	555663	1:60	BD Pharmingen
BDCA1 (CD1c)	AD5-8E7	IgG2a mouse	130-090-695	1:20	Miltenyi Biotec
BDCA-2 (CD303)	AC144	IgG1 mouse	130-090-690	1:20	Miltenyi Biotec
BDCA-3 (CD141)	AD5-14H12	IgG1 mouse	130-090-694	1:20	Miltenyi Biotec
BDCA-4 (CD304)	AD5-17F6	IgG1 mouse	130-090-693	1:20	Miltenyi Biotec
CD1a	010	IgG1,k	M3571	1:20	Dako Cytomatic
HLA-DR	G46-6	IgG2a,k mouse	555810	1:100	BD Pharmingen
DC-LAMP (CD208)	104.G4	IgG1 mouse	IM3448	1:100	Immunotech

Table III. *Summary of the scoring system used for the quantification of immunolabeled cell numbers.*

Score	*Number of cells*
0	0
1	1-3
2	4-6
3	7-9
4	> 10

HLA-DR, Langerin, CD83, CD86, CD1a, BDCA1, BDCA2, BDCA3, BDCA4 and DC-LAMP immunoreactive cells were counted under light microscopy in a rectangular area (0,125 x 0,25 mm²) of epidermis, papillar and reticular dermis at 400 x magnification and finally put in an appropriate range. A range from 0 to 4 was used. The absence of immune reaction were scored as "0", more than 10 immunolabeled cells was scored as "4".

between the two molecules.

Langerin+DCs (LCs) were increased in number in the epidermis and in the derma of lesional skin and their number was reduced after biological therapies. Our results clearly demonstrate an increase in LCs in psoriasis, underscoring the importance of these cells in the pathogenesis of this disease. However, several investigations have reported conflicting results related to the number of LCs in lesional skin, as LCs were reduced according to some Authors and increased according to others (12). One possible explanation for this discrepancy could be related to different LC numbers in different stages (more or less infiltrated) or sites of psoriatic plaques

The present findings concur with recent studies in psoriatic patients, showing strong Langerin immunostaining in the dermis, to account for the existence of a novel population of LCs, the dermal LCs (dLCs), distinct from the traditional epidermal LCs that can traffic from the skin to draining lymph nodes. The dLC population diverges from epidermal LCs not only for its anatomical distribution but also for the lack of some phenotypic markers, Ep-CAM, and CD11b Dectin-1 and for the positive expression of CD103 integrin (13). In a functional perspective, dLCs may offer an additional contribution to skin immune responses, as they could recruit additional inflammatory APCs that can induce TC responses after migration to lymph nodes. If not activated, dLCs are difficult to identify due to the absence of specific markers.

Within psoriatic plaques there are a large number of dermal dendritic cells (dDCs) immediately beneath the hyperplastic epidermis surrounded by T cells. In addition dDCs possess a potent capability to induce proliferation of resting TCs mediated by involvement of HLA-DR and lymphocyte-function-associated antigen 1 (LFA-1) molecules and associated with high levels of Interleukin (IL)-2 and IFN-γ production.

Our data show a significant increase in mDCs in psoriatic skin before treatment and a strong decrease after biological therapies (a reduction of 70% for CD83+ DCs). The functional importance of increased presence of mDCs in psoriasis, both immature and mature, consists in the fact that these

Table IV. *Statistical results immunolabeling scores "before" and "after" treatment with biological therapy samples.*

	Epidermis		*Papillar dermis*		*Reticular dermis*	
	Before therapy	**After therapy**	**Before therapy**	**After therapy**	**Before therapy**	**After therapy**
	Mean	*Mean*	*Mean*	*Mean*	*Mean*	*Mean*
Langerina	4	2	4	1	2	1
CD83	2	1	2	1	2	1
BDCA-1		1	2	1	2	2
BDCA-2	2	1	3	1	2	1
BDCA-3		1	3	2	4	1

cells are strong activators of type 1 TC responses. In our samples, immature subsets differentiate *in situ* into mature DCs as judged by the strong expression of differentiation markers (CD83, DC-LAMP) and co-stimulatory antigens (as CD86). Remarkable numbers of DCs in the lesional epidermis were positive for these markers, suggesting that some DCs in psoriatic skin express the co-stimulatory and differentiation molecules required for antigen presentation. In turn, differentiation is surely enhanced or reinforced *in situ* by the large amounts of cytokines secreted in the psoriatic microenvironment. Recently, CD83+DCs in psoriatic lesion have been reported to produce TNF-α, which can activate DCs, keratinocytes and other cell-types to express iNOS and generate nitric oxide (14).

BDCA-2+DCs, the pDCs, were only detected in the lesional skin of psoriatic plaques, but not in the perilesional skin, in the uninvolved skin or in the distant skin; pDCs are reported to play a critical role in the initiation of psoriatic lesions (15). In fact pDCs are key to innate immunity but are capable of driving Th1 responses, also affecting adaptive immunity; they are particularly abundant in viral-type infections for their well documented activity to produce Interferon-α (IFN-α) (16). Recently, these cells have been also described in sentinel lymph nodes of melanoma patients and in metastatic nodes (17) supporting that pDCs can shift immune response toward a Th2 pattern, which favors tumor progression. Furthermore, pDCs are able to induce proliferation of CD8+ TCs, which produce Interleukin (IL)-10(18), a strong immunosoppressive cytokine able to modify the APC capability of DCs. This latter property, besides IFN-α production (19) can help explain the key roles played by pDCs in psoriasis.

The higher decrease in immature and mature DCs by Raptiva compared to Enbrel in psoriatic plaques may be conceivably linked to the interaction between CD11a/CD18, blocking the ICAM-1/LFA-1, but also to inhibitory signals on cytokine production by DCs, particularly IL-12 and IL-23. These cytokines have been detected at elevated levels in psoriasis lesions, where they may augment IFN-γ production from TCs and stimulate clonal expansion of type-1 TCs. Moreover, the reduction of CD83+ and LAMP+ DCs can reduce the juxtaposition of TCs and mature DCs in dermal aggregates and the local production of lymphoid-organizing chemokines, such as CCL19 and CCL 21 (20), thus further inhibiting the activation of TCs *in situ* and the amplification of the inflammatory pathway.

Another interesting finding of our study is the different percentage of HLA-DR+ DCs in patients treated with anti-CD11a versus anti-TNF-α (score 3 vs. score 2). HLA-DR is one of the MHC II molecules, expressed on activated keratinocytes and mononuclear cells (21); its expression is enhanced when DCs are activated and become mature, being needed for antigen presentation (22). The primary function of HLA-DR is to present peptidic antigens to the immune system; DCs, as members of the APC family, typically express HLA-DR. Antigens are internalized, processed intracellularly, re-exposed at the cell surface bound to the HLA-DR complex and presented to a few TCs bearing the specific receptors. Moreover, preservation of HLA-DR molecules at the plasma membrane of DCs is an established marker of healthy immunological status and of active immune recognition; tumour cells or de-differentiated cells tend to lose their HLA-DR molecules early along with their dedifferentiation process.

REFERENCES

1. Steinman M, Cohon ZA. Identification of a novel cell type in peripheral lymphoid organs in mice. J Exp Med 1973; 137:1142-53.
2. Kissenpfennig A, Ait-Yahia V, Cleir-Moninot H, et al. Mol Cell Biol 2005; 25:88-9.
3. Krueger GG, Bergstresser PR, Lowe NJ,Voorhees JJ, Weinstein GD. Psoriasis. J Am Acad Dermatol 1984; 11:937-46.
4. Guilhou JJ, Meynadier J, Clot J. New concepts in the pathogenesis of psoriasis. Br J Dermatol 1978; 98: 585-92.
5. Abrams JR, Kelley SL, Hayes E, et al. Blockade of T lymphocyte costimulation with cytotoxix T-lymphocyte-associated antigen 4-immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. J Exp Med 2000; 192:681-94.

6. Bos JD, de Rie MA, Teunissen MB, Pskin G. Psoriasis:dysregulation of innate immunity. Br J Dermatol 2005; 152:1098-107.
7. Bowcock AM, Krueger JG. Getting under the skin: the immunogenetica of psoriasis. Nat Rev Immunol 2005; 5:699-711.
8. Chamian F, Krueger JG. Psoriasis vulgaris: an interplay of T lymphocytes, dendritic cells and inflammatory cytokines in pathogenesis. Curr Opin Rheumatol 2004; 16:331-7.
9. Jariwala SP. The role of dendritic cells in the immunopathogenesis of psoriasis Arch Dermatol Res 2007; 299:359-66.
10. Banchereau J, Briere F, Caux C, Davoust J, Labecque S, Liu Y, Pulendran B, Palucka K. Immunobiology of dendritic cells. Ann Rev Immunol 2000; 18:767-811.
11. Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. Ann Rheum Dis 2005; 64:30-6.
12. Deguchi M, Aiba S, Ohtani H, Nagura H, Tagami H. Comparison of the ditribution and numbers of antigen-presentng cells among T-lymphocyte-mediated dermatoses: CD1a, factor XIIIa+, and CD68+ cells in eczematous dermatitis, psoriasis, lichen planus and graft-versus-host disease. Arch Dermatol Res 2002; 294:297-302.
13. Bursch LS, Wang L, IgyartoB, et al. Identification of a novel population of Langerin^{+} dendritic cells. JEM 2007; 13:3147-3156.
14. Lowes MA, Chamian F, Abello MV, et al. Increase in TNF-alpha and inducible nitric oxide synthase-expressing dendritic cell in psoriasis and reduction with efalizumab. Proct Natl Acad Sci USA 2005; 102:19057-62.
15. Wollenberg A, Wagner M, Ghunther H, et al. Plasmacytoid Dendritic Cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. J Invest Dermatol 2002; 119:1096-102.
16. Nestle FO, Conrad C, Tun-Kyi A, Homey B, et al. Plasmacytoid dendritic cells initiate psoriasis through interferon-α production. JEM 2005; 202: 135-43.
17. Gerlini G, Urso C, Borgognoni L, et al. Plasmacytoid dnedritic cells represent a major dendritic cell subset in sentinel lymph nodes of melanoma patents and accumulate in metastatic nodes. Clin Immunol 2007; 125:184-93.
18. Gilliet M, Liu YJ. Generation og human CD8 T regulatory cells by CD40 ligand-activated plasmacytoid dendritic cells. J Exp Med 2002; 195: 695-704.
19. Funk J, Langeland T, Schrumpf E, Hanssesn LE. Psoriasis induced by interferon-alpha. Br J Dermatol 1992; 125:463-4.
20. Zhou X, Krueger JG, Kao MC, Lee E, Du F, Menter A, Wong WH, Bowcock AM. Novel mechanisms of T-cell and dendritic cell activation revealed by profiling of psoriasis on the 63, 100 element oligonucleotide array. Physiol Genomics 2003; 13: 69-78.
21. Griffiths CE, Voorhees JJ, Nickoloff BJ. Characterization of intercellular adhesion molecule-1 and HLA-DR expression in normal and infame skin: modulation by recombinant gamma interferon and tumor necrosis factor. J Am Acad Dermatol 1989; 20:617-29.
22. Lutz MB, Schuler G. Immature, semi-mature and fully mature dendritic cells: which signals induce tolerance or immunity? Trends Immunol 2002; 23: 445-9.