

Review Article

Pathogenesis of psoriasis

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Abstract Psoriasis is a common, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role. The disease had been traditionally considered as a hyperproliferative disorder and various treatment modalities supposedly had anti-proliferative actions. Recently the advances in molecular techniques have given a new view regarding the pathogenesis of the disease. Now there is considerable evidence to suggest that psoriasis is a T-cell mediated inflammatory disease and various treatment options are now becoming available which effect different steps of this immune mechanism. Considering the importance of psoriasis it is considered mandatory to review the recently revised pathogenesis of the disease along with a brief description of the mechanism of action of various biological agents which are being used in the treatment.

Key word

Psoriasis, pathogenesis, immunity, inflammation, T lymphocytes, biological agents.

Introduction

The pathogenesis of psoriasis has changed dramatically over the past decade. Previously it was assumed that keratinocyte proliferation associated with abnormal epidermal differentiation was the primary cause. However, it is now recognized that epidermal hyperplasia is a reaction to activation of immune system in focal regions, which in turn is mediated by CD8⁺ and CD4⁺ T lymphocytes that accumulate in the diseased skin. Indeed psoriasis is now recognized as the most prevalent T-cell mediated inflammatory disease in humans.¹

There are three cardinal features of lesional psoriatic skin:

1. Epidermal hyperproliferation with loss of differentiation.
2. Dilatation and proliferation of dermal blood vessels.
3. Accumulation of inflammatory cells, particularly neutrophils and T-lymphocytes.

The following account will discuss in detail the various pathogenic mechanisms, which contribute to the above changes.

Molecular genetics

As a result of various genetic studies eight loci have been identified which are linked to the pathogenesis of psoriasis. These loci and their location at various chromosomes are given in **Table 1**.

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Table 1: Genetic loci significantly linked to Psoriasis

Designation	Chromosomal locus	References
<i>PSORS 1</i>	6p21.3	3
<i>PSORS 2</i>	17q	4
<i>PSORS 3</i>	4q	5
<i>PSORS 4</i>	1q	6
<i>PSORS 5</i>	3q	7
<i>PSORS 6</i>	19q	8
<i>PSORS 7</i>	1p	9
<i>PSORS 8</i>	16q	10

PSORS: Psoriasis susceptibility locus; p: short arm of a chromosome; q: long arm of a chromosome

Among all the genetic loci mentioned in **Table 1**, *PSORS 1* is undoubtedly the major genetic determinant of psoriasis, perhaps accounting for 30-50% heritability of psoriasis.² It is located within the major histocompatibility complex (MHC) on the short arm of chromosome 6. The exact mechanism by which *PSORS 1* interacts with other genes and the environment in causation of psoriasis is not known. With respect to *PSORS 1* it appears that psoriasis vulgaris is genetically identical to guttate psoriasis and distinct from palmoplantar pustular psoriasis.

Epidermal proliferation

As the clinical appearance of psoriasis is largely caused by epidermal changes, the disease has traditionally been considered as a disorder associated with excessive keratinocyte proliferation and abnormal differentiation.¹¹ Within the psoriatic lesions the keratinocyte cell cycle time is reduced by approximately 8-folds (36 vs. 311 hours in normal skin).¹² It is now proved by several studies that increased keratinocyte proliferation in psoriasis is due to increase in the proliferating cell compartment in the

basal and suprabasal level and not because of shortened cell cycle time. The number of cycling cells is increased approximately seven folds.¹³ Several growth factors, which experimentally have been shown to modulate keratinocyte proliferation, are present in the lesional skin.¹⁴ In particular transforming growth factor- α (TGF- α) appears to be an important autocrine mediator of this event.¹⁵

Vascular changes

Vertical dermal capillary loops in the lesional skin of psoriasis patients are dilated, elongated and twisted. Image analysis demonstrates four fold increase in endothelium in superficial microvasculature.¹⁶ These vascular changes occur early in the development of the lesions.¹⁷ It has been demonstrated that the main signals for angiogenesis are generated primarily from the keratinocytes.¹⁸ These signals are in the form of several chemokines such as interleukin-8 (IL-8), tumour necrosis factor- α (TNF- α), thymidine phosphorylase, endothelial cell stimulating angiogenesis factor and most importantly vascular endothelial growth factor (VEGF).¹⁹ Circulating VEGF has been detected in patients with erythrodermic and severe plaque psoriasis, which correlates with the level of proteinuria in these patients.²⁰

In addition to the vascular growth, dermal capillaries contribute actively in the inflammatory process through surface expression of molecules involved in leucocyte movement into the skin. Importantly E-selectin is induced and intracellular adhesion molecule-1 (ICAM-1)

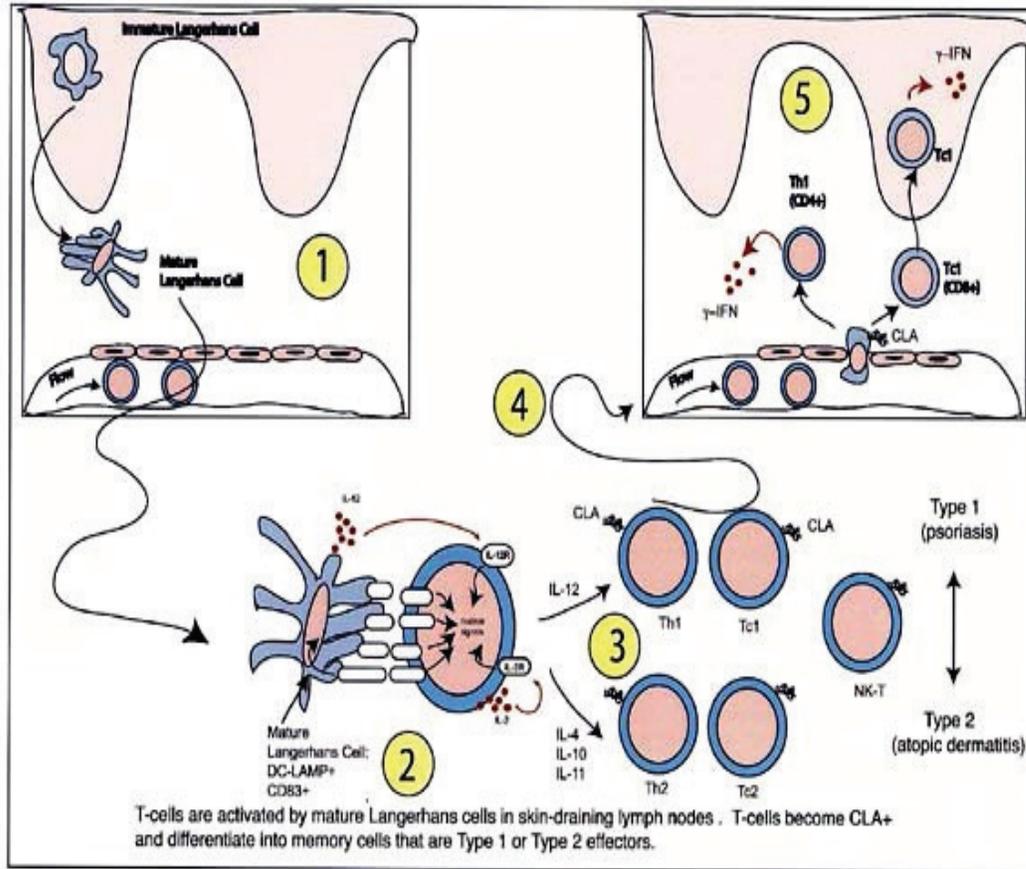


Figure 1 Various steps in the generation of T-cell based inflammatory response in the psoriatic skin [14].

is upregulated on dermal vessels in the lesional skin. These receptors provide a mechanism for the skin homing T lymphocytes to accumulate within the dermis and epidermis of the lesional skin.²¹

Immunology and inflammation

There are now considerable evidences that T lymphocytes have an important role in the pathogenesis of psoriasis. This is evident from the following facts:

1. Before antibodies became available to phenotype different types of leukocytes, it was evident that in the dermis of the lesions of psoriasis vulgaris there were numerous mononuclear inflammatory cells (leukocytes), and that these cells

appeared in early lesions before obvious epidermal changes were apparent.²²

2. In 1978, T lymphocytes and macrophages were identified as the chief cell types in these dermal infiltrates through cell-binding assays.^{23,24}
3. By 1983, monoclonal antibodies were available to more precisely phenotype the infiltrating leukocytes in psoriasis lesions. Studies at that time showed accumulations of both CD4+ and CD8+ T lymphocytes, increased dermal Langerhans cells, and scattered dermal monocytes (macrophages).²⁵
4. This view was further supported by the finding that epidermal keratinocytes in psoriatic lesions synthesize human leukocyte antigen (HLA)-DR molecules.²⁶

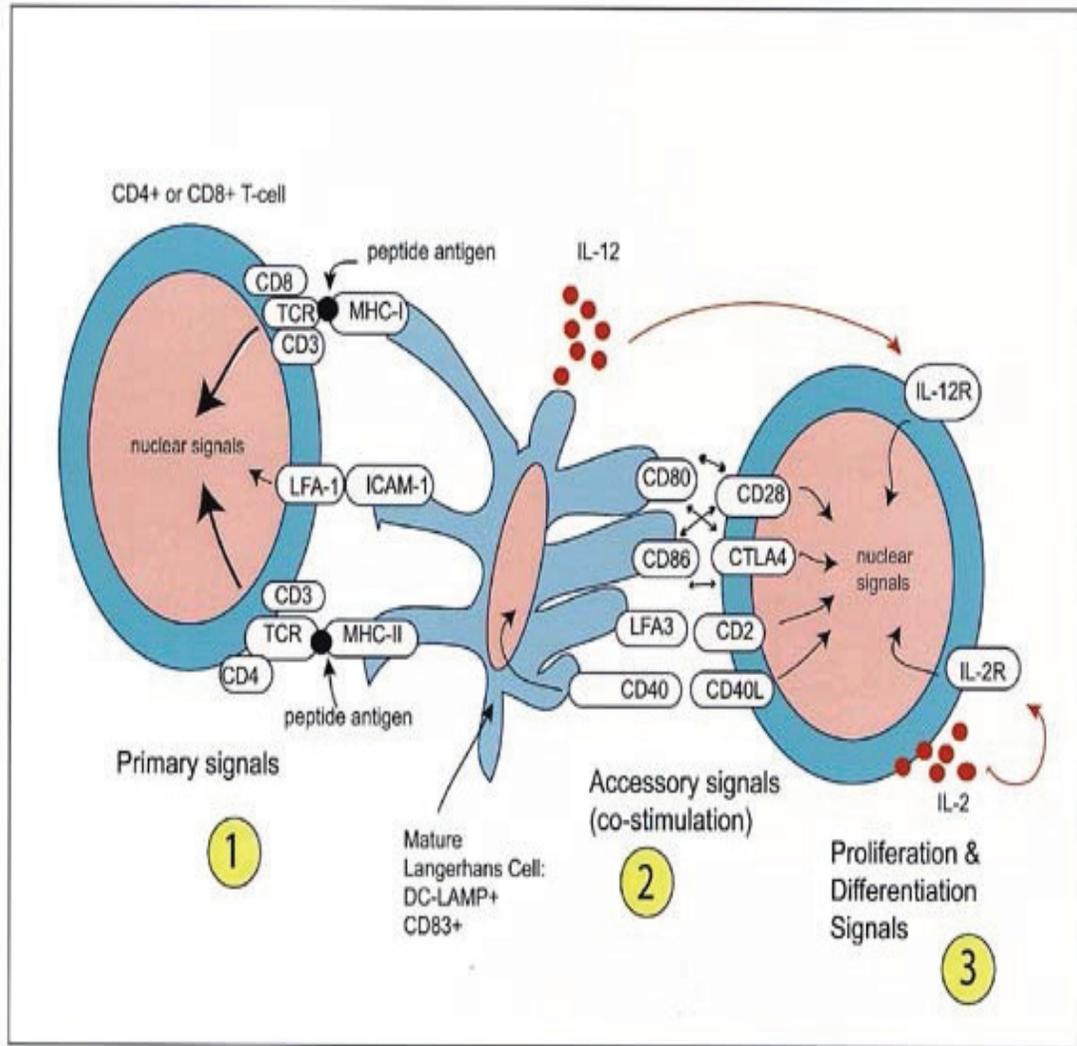


Figure 2 Various steps of the T-cell activation [14].

5. PUVA therapy depletes lymphocytes from the skin and hence brings improvement in skin lesions.^{27,28}
6. Cyclosporine has a major inhibitory effect on T-cell activation, and the improvement thus caused supports the idea that psoriasis is fundamentally an inflammatory disease.²⁹ However, cyclosporine also has strong antiproliferative effects on epidermal keratinocytes at therapeutic concentrations.^{30,31} In addition, FK506 (a T-cell selective immunosuppressant,

like cyclosporine) was also found to be effective in psoriasis.³²

7. Finally, in a laboratory experiment, psoriatic lesions were induced in the normal-appearing skin in a patient of psoriasis by intradermal injection of peripheral blood mononuclear cells (primarily T lymphocytes) after they were activated with bacterial super antigens.³³ In this experiment neutrophils were absent from induced lesions, suggesting that their role is secondary in initiation of psoriasis skin lesions.

Cellular and molecular events in activation of cutaneous immune system as regards to the causation of psoriasis

Following account is a sequential presentation of various biological and molecular events that ultimately result in the initiation and progression of psoriasis.

1. Antigen driven maturation of antigen presenting cells (APCs)

- (a) Skin contains large number of APCs. In epidermis they are called Langerhans cell and in dermis, dermal dendritic cells. Langerhans cells exist in immature state and are unable to activate T-cells.
- (b) Once the Langerhans cells internalize some macromolecules, it is enzymatically processed and the antigen is presented on the surface of the APCs for presentation to naïve T cells.³⁴ This process is called maturation.
- (c) The process of APCs maturation would lead to uptake and processing of the antigen peptides in such a way that they are associated with extracellular major histocompatibility antigen (MHC) molecules.
- (d) Maturation in APCs is associated with an increased synthesis of cell-surface counter receptors including CD80, CD86, CD40, and intercellular adhesion molecule (ICAM)-1. The proteins DC-LAMP and CD83 are also induced during maturation and are expressed only by fully mature Langerhans cells.
- (e) In the course of normal cutaneous immune reactions the antigens are eliminated by an immune mechanism appropriate to that antigen, e.g. macrophages activated by cytokines

removes the bacterial antigens, the dermal antigens are eliminated by antibodies stimulated in part by cytokines released from T-helper cells (T_H2 cells) and viral antigens are removed by cytotoxic T lymphocytes (CTLs) and/or interferon produced by activated T-cells (T_H1 cells).

- (f) In chronic plaque psoriasis the immune response is somehow sustained in focal skin region. This is evident by the presence of abundant numbers of mature Langerhans cells in the epidermis and dermis.³⁵ One hypothesis is that bacterial superantigens initiate the process, and the molecular mimicry between bacterial protein and keratin 17 leads to maturation of Langerhans cells and generation of autoreactive T cells and thus the disease persistence.³⁶

2. Migration of antigen bearing Langerhans cells to skin draining lymph nodes

The activated dendritic APCs then migrate to skin draining lymph nodes where the naïve T-cells are concentrated (**Figure 1**, Step 1).

3. T-cell activation

The activation of T-cells in conjunction with mature APCs is a multi-step process. The sequence of activation events can be termed as primary stimulation, co-stimulation and mitotic stimulation (**Figure 1**, Step 2).

(a) Primary stimulation

- (i) The initial event is the recognition of the antigen peptide that are bound to either MHC-I for intracellular

antigens and MHC-II for extracellular antigens on APCs.

- (ii) The antigens are recognized by T-cell receptor (TCR) complex present on the surface of T-cells. Antigen presented on MHC-I is recognized by TCR/CD3/CD8 complex, whereas antigen present on MHC-II is recognized by TCR/CD3/CD4 complex.¹ (**Figure 2**, Step 1).
- (iii) Lymphocyte function associated antigen-1(LFA-1), which is an integrin (composed of CD11 and CD18 subunits) present on the T-cells, and ICAM-1 located on the APCs maintain the adhesion between the T-cells and APCs (1) (**Figure 2**, Step 1).

(b) *Accessory or co-stimulation*

- (i) This is achieved by an interaction between CD28 on T-cell surface with CD80 and CD86 on the surface of APCs (**Figure 2**, Step 2).³⁷
- (ii) The coordinated stimulation of TCR and CD28 regulate the transcription of several cytokines involved in T-cell activation. These include IL-2, TNF- α , interferon- γ (IFN- γ) and granulocyte-macrophage colony stimulating factor (GM-CSF).^{38,39}
- (iii) There are other accessory or co-stimulation counter-receptors including ICAM-1/LFA-1, LFA-3/CD2 and CD40/CD40L (**Figure 2**, Step 2).⁴⁰

(c) *Mitotic stimulation*

- (i) Signals delivered to T-cells from the cytokines IL-2 (made by activated T-cells) and IL-12 (made by mature Langerhans cells) regulate the mitotic activation and differentiation of T-

cells into type-1 effector cells (**Figure 2**- Step 3)

- (ii) The early steps in APCs maturation appear to be controlled by antigen capture and by cytokines such as GM-CSF, IL-4 and TNF- α .^{41,42} In later stages the maturation is regulated through the contact with T-cells. Hence the interaction between CD40 on APCs and CD40L on activated T-cells not only enhances T-cell activation and differentiation but also stimulates the dendritic cell survival and activity.⁴³

4. T-cell proliferation and differentiation

- (a) After activation, T-cells clonally proliferate and differentiate into either T γ 1 (CD4+) or T γ 1 (CD8+) effector T-cells that produce type-1 cytokines such as IFN- γ , IL-2 and TNF- α . (**Figure 1**, Step 3).⁴⁴
- (b) A second pathway of T-cell maturation generates T γ 2 (CD4+) or T γ 2 (CD8+) effector T-cells that release type-2 cytokines, which include IL-4, IL-6 and IL-10. A high concentration of type-2 cytokines suppresses the action of the type 1 effector T-cells, while increases the immunoglobulin production from B-cells.⁴⁵
- (c) Finally T-cells also differentiate into natural killer (NK) T-cells, which are cells that can react to some non-protein antigens.⁴⁶

Psoriasis is considered as type-1 disease characterized by secretion of type-1 cytokines and a predominance of CD8+ T-cells in epidermis and CD4+ T-cells in the

dermis.⁴⁷ Both CD4⁺ and CD8⁺ T-cells produce mainly type-1 cytokines.⁴⁸

5. Movement of CLA⁺ T-cells into the inflamed skin

- (a) During maturation T-cells express new surface proteins that enable them to exit from the blood vessels and migrate into the inflamed skin.⁴⁹ The most important trafficking protein on memory T-cells is a glycoprotein termed as cutaneous lymphocyte associated antigen (CLA). T-cells in the inflammatory diseases not involving the skin are CLA negative.⁵⁰
- (b) CLA is not just a marker of skin specificity. It is an adhesion molecule that mediates the initial ‘tethering’ of T-cells to the endothelium in the cutaneous post-capillary venules.⁵¹
- (c) After ‘tethering’, the T-cells roll slowly on the endothelial surface (**Figure 1**, Step 4), allowing them to be exposed to several chemokines. These chemokines are secreted by keratinocytes, monocytes and Langerhans cells in the skin under the influence of IFN- γ and TNF- α produced from the activated T-cells (**Figure 1**, Step 5)

6. T-cell mediated inflammation in skin lesions

- (a) As T γ 1 and T δ 1 T-cells enter the dermis from cutaneous vasculature, they release high levels of IFN- γ and TNF- α .
- (b) These cytokines induce ICAM-1, CD40 and MHC-II proteins on the epidermal keratinocytes. The

detection of HLA-DR (MHC-II) molecules on the epidermal keratinocytes in psoriatic plaques is a proof that T-cell products contribute to pathologic changes in the keratinocytes.⁵²

- (c) The intraepidermal T-cells trigger keratinocyte hyperproliferation, which accelerates epidermal growth.⁵³ Some inflammatory cytokines (e.g. IL-1 and IL-6) have been shown to be direct keratinocyte mitogens, so elaboration of cytokines from intraepidermal T-cells could directly stimulate keratinocyte proliferation. Some in-vivo studies have shown IFN- γ as a trigger of epidermal hyperplasia, which is however, somewhat less in psoriasis.⁵⁴ Hence other mechanisms are also involved in the stimulation of keratinocyte proliferation.
- (d) One such mechanism is the disruption of desmosomes between the keratinocytes by the migrating lymphocytes in the epidermis.¹ The basement membrane is also destroyed due to the leukocyte migration.⁵⁵ The disruption of desmosomes and basement membrane is viewed by the keratinocytes as ‘injury’ and induces ‘injury response’. This response includes stimulation of numerous mitogenic cytokines and receptors on the surface of keratinocytes. These cytokines stimulate keratinocytes hyperproliferation. By the ongoing release of inflammatory cytokines from activated T-cells and continuous migration of activated T-cells in the epidermis, there is a continuous set of signals of chronic epidermal hyperplasia in psoriatic lesions.

- (e) The release of inflammatory cytokines from the activated T-cells triggers the differentiated keratinocytes to synthesize and release IL-8.⁵⁶ This cytokine probably serves as main chemotactic signal for attraction of neutrophils into the epidermis from the vascular stores. The persistence of neutrophils in the epidermis in the lesions of psoriasis is a proof of the fact that there is an ongoing trafficking of these cells into the epidermis with a potential to further injure the basement membrane and desmosomes, and hence generating continuous signals for keratinocyte proliferation.

Immune-altering biological therapy in psoriasis

Although the treatment aspect of psoriasis is beyond the scope of this article, a brief description of several new biological agents, which are being used in the treatment of psoriasis, is given below. Their mechanism of action will be better understood in view of the description of the immunological basis of the disease given above.

1. Efalizumab (Raptiva), humanized anti-CD11a

As LFA-1 (composed of CD11&CD18 subunits) and ICAM-1 binding is the initial interaction between T-cell and Langerhans cell (**Figure2**, Step 1), blockage of this interaction by humanized anti-CD11a will prevent the binding between T-cell and Langerhans cell.¹

2. HuM291 (Humanized anti-CD3 monoclonal antibody)

As CD3 is an important component of TCR complex (**Figure2**, Step1), which is required for the recognition of the antigen present on the APCs. After the binding of HuM291 to the CD3, TCR complex is only partially activated, resulting in reduced inflammatory reaction and masking of the effects of the disease.⁵⁷

3. Humanized anti-CD4 monoclonal antibodies

More recent studies have reported reduction in psoriatic lesional area in patients after therapy with humanized anti-CD4 monoclonal antibodies, as a result of reduction in both CD4+ and CD8+ T-cells (**Figure1**, Step5).^{58,59}

4. CTLA4Ig

This is a fusion protein that combines CTLA4 and IgG heavy-chain. It is demonstrated that this fusion protein blocks CD80 and CD86 receptors on APCs (**Figure 2**, Step 2), resulting in decreased T-cell co-stimulation and improvement of psoriasis lesions.⁶⁰

5. Alefacept

It is an LFA-3Ig fusion protein that binds to CD2 on T cells (**Figure2**, Step2). This results in blockage of co-stimulation and significant depletion of circulating memory T-cells. Alefacept has demonstrated encouraging activity in phase II trial in 299 patients with moderate to severe psoriasis.⁶¹

6 *Daclizumab (Zenapax) and Basiliximab (Simulect)*

The proliferation of T-cells after activation is largely under control of IL-2 (**Figure 2**, Step 3). IL-2 binds to α -protein subunit (termed CD25) of IL-2 receptors to exert its effect. A blockage of CD25 by Daclizumab, correlate with the reduction in disease severity.⁶² Basiliximab is another agent targeting CD25, has also proved to be effective in severe psoriasis in small case studies.^{63,64}

7. *DAB₃₈₉IL-2 fusion protein (Denileukin Diflitox)*

This molecule specifically binds to IL-2 receptors. After the receptor-mediated endocytosis this molecule releases enzymatic fragments of diphtheria toxin that inhibit the protein synthesis and eventually leading to apoptosis of the T-cells. Its clinical trials have given promising results in psoriasis.^{65,66}

8. *Neutralizing antibodies to IL-12*

IL-12 secreted by APCs has a positive mitogenic_influence on T-cells by IL-12 receptor on the activated T-cells (67) (**Figure2**, Step3). By blocking IL-12 by the neutralizing antibodies, this step in T-cell differentiation can be significantly suppressed.

9. *Manipulation of T-cell differentiation by recombinant cytokines (“immune deviation”)*

The manipulation of the T_H1/T_H2 and Tc1/Tc2 balance by exogenously administered cytokines is a therapeutic strategy generally termed as “immune deviation”. In psoriasis, the type-1

cytokine-producing T-cells are potentially suppressed by the production of type-2 cytokines by the administration of exogenous IL-4, IL-10, or IL-11, (**Figure1**, Step3) and bring improvement in the disease. In a recent phase II trial, recombinant IL-10 was administered to 10 patients with psoriasis over a 7-week period,^{68,69} and significant antipsoriatic effects were demonstrated in 9 patients.

10. *HuZAF (humanized IgG1 antibody against human IFN- γ)*

Much of pathogenic inflammation in psoriasis is potentially due to the release of IFN- γ from activated T-cells (**Figure1**, Step5). Blockage of this cytokine is beneficial in the way that it does not cause global immunosuppression. The clinical studies in patients of psoriasis are in progress (1).

11. *Infliximab (Remicaide) and Etanercept (Enbrel)*

Like IFN- γ , TNF- α is also an important cytokine that is secreted by activated T-cells, which stimulates the keratinocyte hyperproliferation. Infliximab is a chimeric anti- TNF- α monoclonal antibody and etanercept is a TNF-receptor-Ig fusion protein. Infliximab is found to be effective in a small phase II trial in patients of psoriasis vulgaris.⁷⁰ A trial of etanercept in patients of psoriatic arthritis, brings significant improvement in skin lesions besides alleviation of arthritis.⁷¹

12. Humanized anti IL-8 antibodies

IL-8 that is secreted by differentiated keratinocytes, has a role in recruitment of neutrophils in the lesional skin. This action is blocked by humanized anti IL-8 antibodies, resulting in moderate clinical improvement in psoriasis patients.⁷²

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