Introduction

Psoriasis is a chronic relapsing and recurrent inflammatory skin disease. It is a common skin disorder, affecting about١-٣٪of the population. It is histological characterized by significant epidermal keratinocyte hyperplasia and it has been suggested that impaired epidermal proliferation and keratinocyte differentiation, characterized by sharply defined erythemato-squamous lesion, as well as increased epidermal turnover play a role in pathogenesis of the disease ***(Bowen, 2004; Hanks et al., ٢٠٠٤).***

Vitamin D is produced by UVB in skin and can be also provided by dietary source such as fat fishy. Vitamin D is considered to be the precursor of a hormone ١, ٢٥-dihydroxy-vitamin D which plays a role in biological effect on the skin, such as regulation of cell growth and differentiation, modulation of immune system and even protection against UV radiation. Phototherapy with ultraviolet UV irradiation is an effective treatment for a variety of inflammatory skin diseases such as psoriasis. The therapeutic effect of UVB radiation may be attributed at least in part to UVB-triggered cutaneous synthesis of Vitamin D ***(Lehmann, 2009).***

Vitamin D production in patients with psoriasis is increased less on NBUVB than with broadband UVB phototherapy. One explanation may be that the optimal wavelength for initiation of

Vitamin D pathway is in range of ٢٩٠-٣١٥nm which covered by broadband UVB (٢٨٠-٣٢٠) and by NBUVB (٣١١-٣١٢). That is cause a precursor in skin ٧-dehydrocholesterol to form vitamin D. Which is biologically inert and metabolized in the liver to ٢٥-hydroxyvitamin D the major circulating form of Vitamin D ٢٥(OH)D is activated in the kidney to ١,٢٥dihydroxyvitamin D to regulate calcium , phosphorus and improve psoriasis ***(Lehmann et al., 2007).***

The stimulation of Vitamin D synthesis by PUVA is short-lived. The magnitude of the rise in serum ٢٥(OH) D is not greater even in the early stages, and addition measurement of serum calcium and inorganic phosphate concentrations showed them to be normal. Thus PUVA is unlikely to lead to harmful concentrations of Vitamin D in the blood ***(Branda et al., 1979).***

Vitamin D also play an important part in healing psoriasis which indicates that one explanation for the positive effect on narrowband UVB on psoriasis may be the induction of Vitamin D synthesis in the skin. This Vitamin regulate important cellular functions in keratinocyte and immunocompetent cells because of their anti-proliferate and prodifferentiating effect. Vitamin D are highly effective in treatment of psoriasis vulgaris in addition, the known ant psoriatic effect of UVB light therapy in treatment of psoriasis can be part mediated by synthesis of Vitamin D ***(Osmancevic et al., 2009).***

Aim of the work

The aim of the work is to compare between the effect of systemic PUVA and narrowband UVB on level of serum vitamin D in Psoriatic patients.

An Overview on Psoriasis

Definition of psoriasis

Psoriasis is a common, chronic and recurrent inflammatory disease of the skin characterized by circumscribed, erythematous and dry scaling plaques of various sizes. The lesions are usually covered by silvery white lamellar scales and have a predilection for the scalp, nails, and extensor surfaces of the limbs, umbilical region and sacrum ***(James et al., 2006).***

Epidemiology of psoriasis

Psoriasis is one of the most common chronic inflammatory skin disorders, affecting about ٢٪ of the general population. It also affects both sexes equally and can appear at any age ***(Neimann et al., 2006).***

Precipitating factors

A lot of environmental factors have been shared in precipitating and worsening psoriasis; including staphylococcal infection, drugs, cigarette smoking, alcohol, obesity, stress and cutaneous trauma ***(Setty et al., 2007).***

Pathogenesis of psoriasis

There is evidence that activated T-cells are the primary modulators in the pathogenesis of psoriasis. This is further supported by the fact that increased levels of activated T lymphocytes are present in psoriatic skin plaques and blood of

patients ***(Huang et al., 2001)***. The involvement of T-lymphocytes in the pathogenesis of psoriasis can be described in terms of ٥ responses (Fig. ١) ***(Krueger, 2002; Lee and Cooper, 2006).***

١. Antigen capture by Langerhans' cells:

The initial step in this process is antigen capture by immature Langerhans' cells in the epidermis (Fig. ١, step ١), which then activates maturation and migration of antigen- bearing Langerhans' cells to skin-draining lymph nodes

٢. Molecular interactions between a mature Langerhans cell and a naive T-cell (T-cell activation):

The sequence of activation events can be termed primary stimulation, costimulation, and mitotic stimulation (diagrammed as steps ١, ٢ and ٣ in Fig. ٢).

The primary signal: that triggers T-cell activation is recognition of an antigen that is bound to either major histocomptability complex I (MHC-I) or II MHC-II) on APCs. In the lymph node, the antigen presenting cell (APC) binds reversibly with naïve or resting T-cells through interactions between surface molecules located on both cells, intercellular adhesion molecule-١ (ICAM-١) on APC binds to leukocyte functional associated antigen-١ (LFA-١) on naïve T-cell. Next, the MHC presents the antigen to a T-lymphocyte receptor to begin activation of the T-lymphocyte.

The second signal for T-lymphocyte activation is a cell-cell interaction known as costimulation ***(Lebwohl, 2005)***. Costimulation involves pairing of receptor with ligand on the T-cell. These pairs include leukocyte functional associated antigen-٣ LFA-٣ interacting with cluster of differentiation ٢ (CD٢), B٧ (CD٨٠ and CD٨٦) interacting with CD٢٨, and ICAM-١ interacting with LFA-١ (Fig.١).

The third set of signals delivered to the T-cell is from the cytokines Interleukin ٢ (IL-٢) (made by activated T-cells) and IL-١٢ (made by mature Langerhans cells). Binding of these cytokines to surface receptors expressed on activated T-cells regulates mitotic activation and differentiation of T-cells into type ١ effectors (Fig. ٢, step ٣).

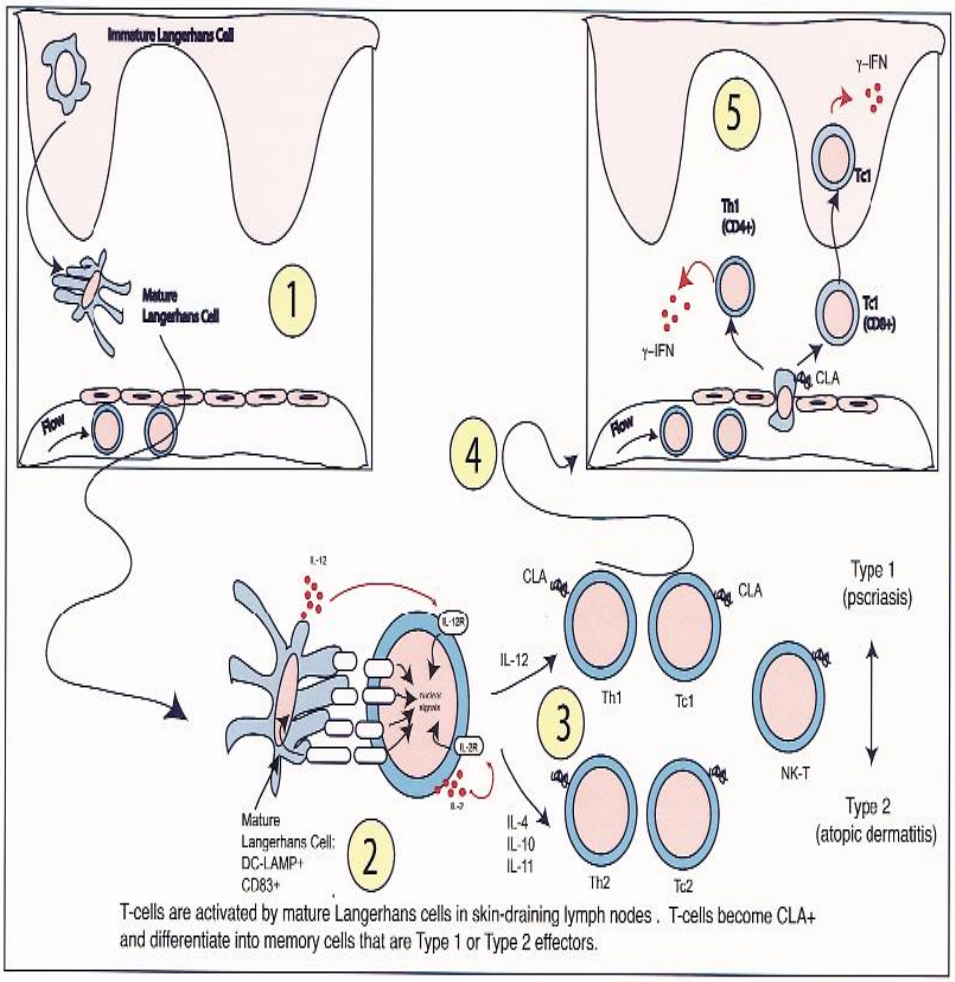

Figure (١): The sequence of cellular immune activation and trafficking pathways of Langerhans cells and T lymphocytes during an immune response ***(Krueger, 2002).***

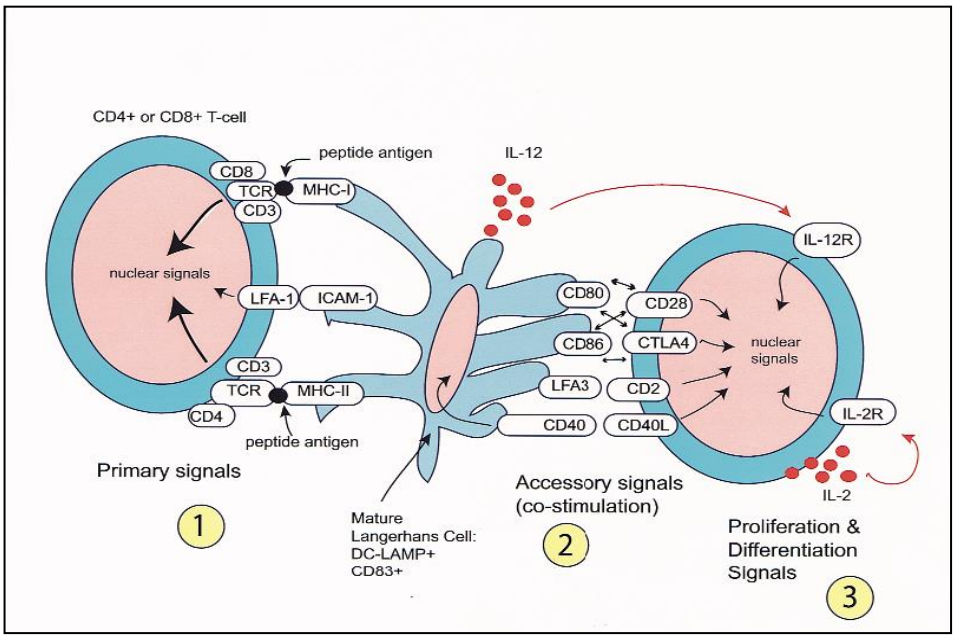

Figure (٢): T-lymphocyte activation by APCs ***(Krueger, 2002).***

٣. T-cell proliferation and differentiation:

Under the influence of IL-١٢ and IFN-γ, CD٤ T-cells differentiate into a Th١ phenotype and CD٨ Tcell differentiates into a Tc١ phenotype that produce type ١ cytokines. Type ١ cytokines include IL-٢, TNF-α and IFN-γ ***(Lee and Cooper, ٢٠٠٦).***

This response is associated with increased cell-mediated immunity and diseases such as psoriasis. Alternatively, under the influence of IL-٤, IL-٦ and IL-١٠, CD٤ T-cells differentiate into a Th٢ phenotype and CD٨ T-cells differentiate into a Tc٢ phenotype that produce type ٢ cytokines. These include IL-٤, IL-٥, IL-٦, IL-١٠ and IL-١١. This response is associated with

antibody production and so-called allergic diseases such as atopic dermatitis. Psoriasis is considered a type ١ disease, characterized by type ١ cytokines and a predominance of CD٤ T-cells in the dermis and CD٨ cells in the epidermis.

٤. Cutaneous lymphocytes antigen (CLA+) memory T-cells enter the circulation (T-cell trafficking):

The activated/memory T-cells must then 'home' to the skin where they can exert their effects (Fig. ٣). This is a multistep process that involves interactions between the activated T-cell and endothelium. T-cells activated in skin-draining lymph nodes express a new surface protein known as CLA, an adhesion molecule that allows tethering of T-cells to the endothelium in cutaneous postcapillary venules.

The Cutaneous lymphocytes antigen glycoprotein interacts with E-selectin and P-selectin expressed constitutively at low levels on cutaneous microvessels and are overexpressed during cutaneous inflammation .After tethering, the T-cells roll slowly along the endothelial cells where they are exposed to chemokines that are produced by resident skin cells. The binding of chemokines to specific receptors on T-cells results in modifications of integrins on the T-cell, including LFA-١ and vascular lymphocytic antigen (VLA-٤) so they can bind to ICAM-١ and vascular cell adhesion molecule (VCAM-١), respectively, on blood vessels. In general, the chemokines are stimulated by IFN- γ and TNF-α released from activated T-cells ***(Lee and Cooper, 2006).***

٥. T-lymphocytes in the dermis or epidermis become activated to release cytokines (T-cell reactivation):

After exiting postcapillary venules, Th١ (CD٤+) lymphocytes encounter dendritic cells within the dermis and Tc١ (CD٨+) lymphocytes encounter Langerhans' cells within the epidermis and subsequently release pro-inflammatory cytokines such as TNF-α and IFN- γ. The production of TNF-α is further increased by other cytokines such as IL-١, IL-٢, granulocyte macrophage colony stimulating factor (GM-CSF) and IFN-γ ***(Krueger, 2002; Lee and Cooper, 2006).***

Interleukin٢٣ and TH١٧ have a role on pathogenesis of psoriasis by which they mediate across between activated dermal immunocytes and epidermal keratinocytes. Following a stimulus like trauma in genetically predisposing person ,DCs and macrophage produce IL-٢٣ and TNF-α; together with IL-٦ and TGF-β. These cytokines lead to activation of TH١٧cells.This recognized subset of CD+Tcells produces IL-١٧ and IL-٢٢, accompanied by mononuclear cell production of IL-١٩, IL٢٠ and IL٢٤ ***(Nickoloff, 2007; Zheng et al., 2007)***.

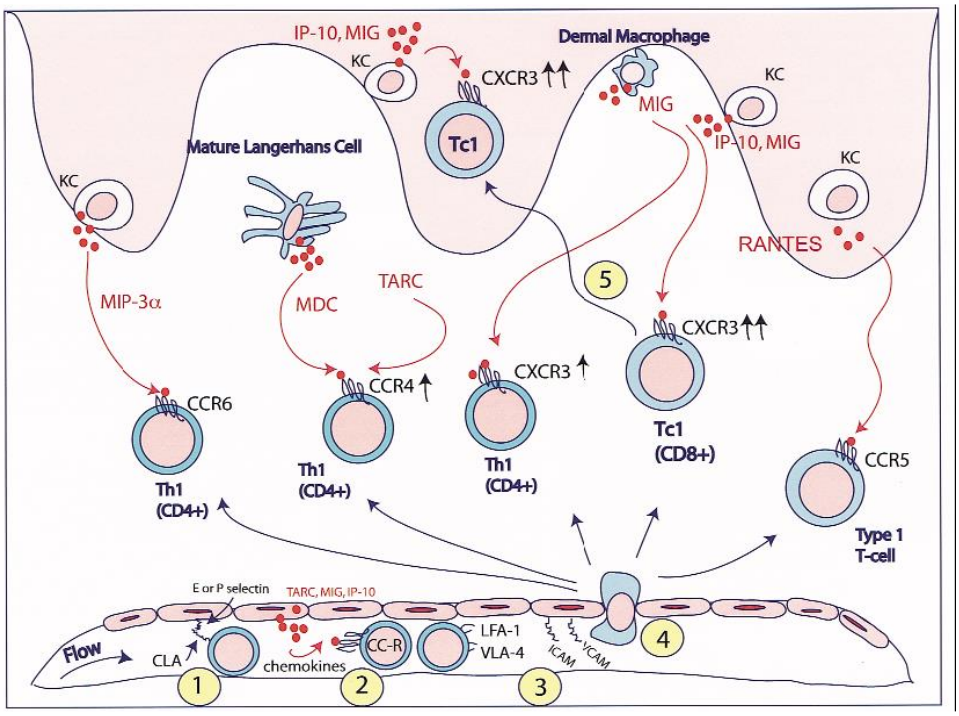

Figure (٣): The migration pathway for skin-homing T-cells in psoriasis ***(Krueger, 2002).***

Table (١): Cytokines produced by T lymphocytes and keratinocytes and their suggested functions in psoriasis ***(Krueger and Ellis, 2005).***

Cell type	Cytokine	Role in psoriasis
T-lymphocytes	IFN-γ	May facilitate keratinocyte hyper-proliferation by inhibiting apoptosis; up-regulates ICAM-١ expression in vascular cells to facilitate T-lymphocyte trafficking
	IL-٢	Stimulates T-lymphocyte growth
	TNF-α	Stimulates production of proinflammatory cytokines from T lymphocytes and macrophages; chemokines from macrophages; adhesion molecules from vascular endothelial cells. Increases proliferation of keratinocytes. Promotes angiogenesis. Up-regulates ICAM-١ expression in vascular cells to facilitate T-lymphocyte trafficking
	Transforming growth factor (TGF-α)	Stimulates proliferation of keratinocytes; acts on keratinocytes to stimulate production of VEGF/VPF to promote angiogenesis and vascular hyperpermeability
Keratinocytes	IL-٦	Stimulates proliferation of keratinocytes
	IL-٨	Stimulates proliferation of keratinocytes; neutrophil chemoattractant
	TGF-α	See above
	Amphiregulin	Stimulates proliferation of keratinocytes; ligand for EGF-R
	TGF-γ	Ligand for Epidermal growth factor receptor (EGF-R)
	IL-١	Up-regulates ICAM-١ expression in vascular cells to facilitate T-lymphocyte trafficking

Management of psoriasis:

Topical therapy which represent an internationally accepted standard therapy for the accompanying treatment of all degrees of acute psoriasis and in interval therapy between systemic or phototherapy courses ***(Nast et al., 2007)***.

Topical corticosteroids such as ١٪ hydrocortisone clobetasol propionate, halobetasolpropionate, betamethasone dipropionate**.** They are available in numerous vehicles including powders, sprays, lotions, solutions, creams, emollient creams, ointments and gels. Corticosteroids are effective as monotherapy or in combination for sequential or rotational treatment. They are effective in short time, simple for use and inexpensive ***(Lebwohl et al., 2005)***.

Tazarotene:

Tazarotene gel, a recently developed topical retinoid for psoriasis, is available in ٠,٠٥٪ and ٠,١٪ gels and creams. Topical retinoids may reverse some of the cutaneous atrophy caused by topical corticosteroids ***(Kaidbey et al., 2001)*** but are associated with local cutaneous irritation. Thus, they are often prescribed in combination with topical corticosteroids ***(Bruner et al., 2003)***.

Topical Calcineurin Inhibitors:

Calcineurin inhibitors are considered as topical immuno-modulators and macrolides. The strength of calcineurin inhibitors is similar to that of a class II corticosteroid. One advantage is that use in corticosteroid-sensitive areas such as the face, skin folds and anogenital region causes no atrophy ***(Freeman et al., 2003).***

Analogs of vitamin D (Calcipotriol): refer to chapter ٢

Older topical treatments:

Older topical remedies of psoriasis such as anthralin and coal tar are still in use. Keratolytic preparations such as those containing salicylic acid and emollients ***(Lebwohl et al., 2005)***.

Systemic Therapy: The more frequently used systemic agents are methotrexate, cyclosporin and acitretin, but fumaric acid esters and hydroxycarbamide are sometimes used, as regarded in table (٢) ***(Khachemoun and Phillips, 2000).***

Table (٢): Systemic agent's used in treatment of psoriasis ***(Khachemoun and Phillips, 2000).***

Approved agents	Therapeutic class	Indications, advantages and monitoring	Major side effects
Acetretin	Retinoids	Very effective therapy for pustular psoriasis. Less effective as a montherapy for plaque psoriasis. Very helpful as an adjuvant to phototherapy	Dry skin and mucous membranes, peeling of palms and soles, alopecia, skin fragility, nail thinning, hyperlipedemia, elevated liver enzymes and teratogenicity
Methotrexate	Antimetabolite (folic acid antagonist)	Highly effective therapy, there is a risk of life threatening heamatological toxicity at any time during therapy and also both acute and chronic hepatotoxicity. Careful monitoring is essential.	Gastrointestinal upset, myelosuppression, hepatotoxicity.
Cyclosporine	Calcineurin inhibitor	Very effective treatment especially helpful for immediate control of severe disease. Less helpful as a long term therapy (>١ year) due to renal toxicity.	Nephrotoxicity, hyper-tension, hirsutism and gingival hyperplasia.

Hydroxyurea	Antimetabolite (purine analogue)	Helpful for patients with cirrhosis who require systemic therapy. Close heamatologic monitoring is essential.	Myelosuppression.
Tacrolimus	Calineurin inhibitor		Nephropathy, parathesia and diarrhea
Thioguanine	Antimetabolite (purine analogue)		Myelosuppression.

Biologics

These biologic agents are proteins that had a pharmacologic activity targeting the inflammatory pathway in psoriasis leading to reduction and inhibition of T-cell activation, immune deviation and blocking the activity of inflammatory cytokines. As regarded in table (٣) (**Ghaffar et al., ٢٠٠٥**).

Table (٣): Summary table of biologics treatment ***(Ghaffar et al., ٢٠٠٥).***

	Alefacept	**Efalizumab**	**Etanercept**	**Infliximab**
Mechanism of action	T-cell targeting	T-cell targeting	TNF-α inhibition	TNF-α inhibition
Method of administration	١٥ mg im (٧,٥ mg iv) weekly for ١٢ weeks	Initial dose ٠,٧ mg/kg, then ١ mg/kg sc weekly	٢٥–٥٠ mg sc twice weekly	٥ mg/kg iv at ٠, ٢ and ٦ weeks, then ٨-weekly
Onset of action	٦–٨ weeks	٢–٣ weeks	٢–٣ weeks	١ week
% of patients with PASI ٧٥	٢٠٪ after ١٢ weeks	٢٥٪ after ١٢ weeks	٣٤٪ with ٢٥ mg; ٤٩٪ with ٥٠ mg at ١٢ weeks	>٨٠٪ at ١٠ weeks