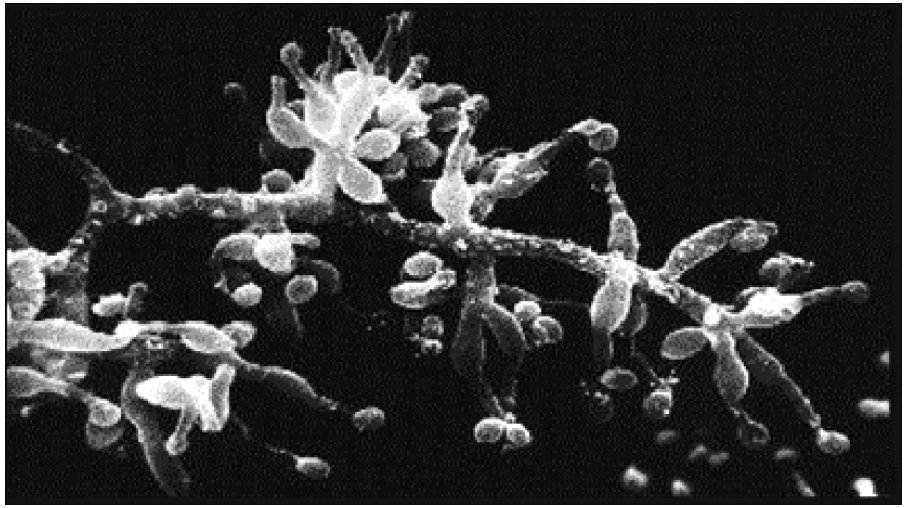
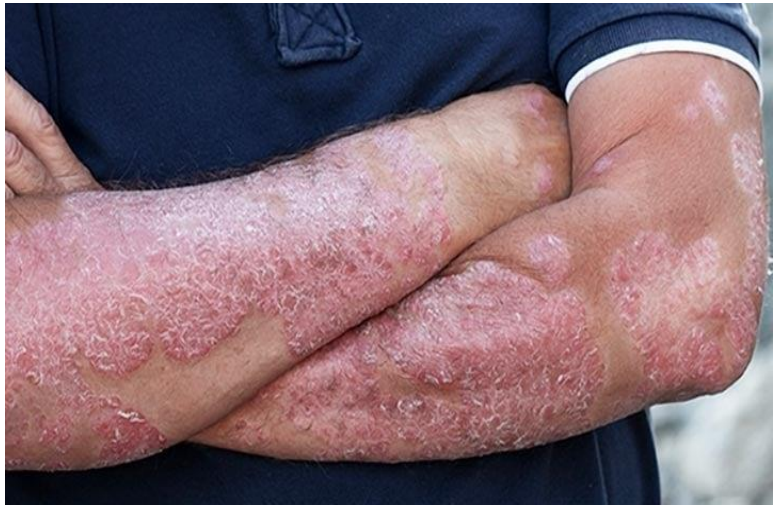
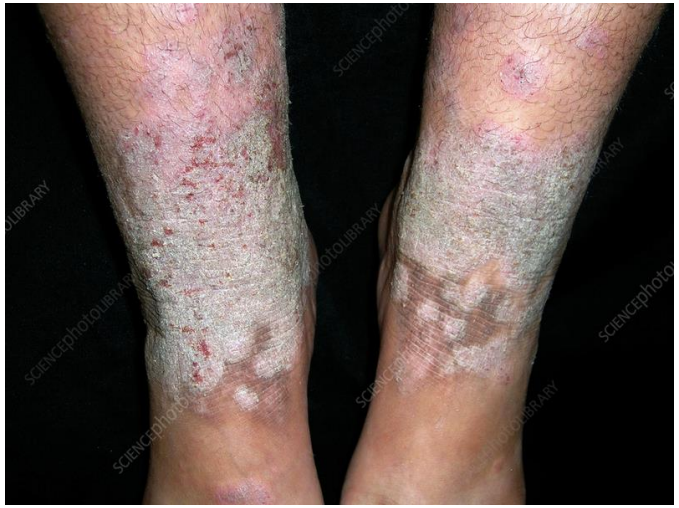
Cyclosporine/Ciclosporin In Dermatology

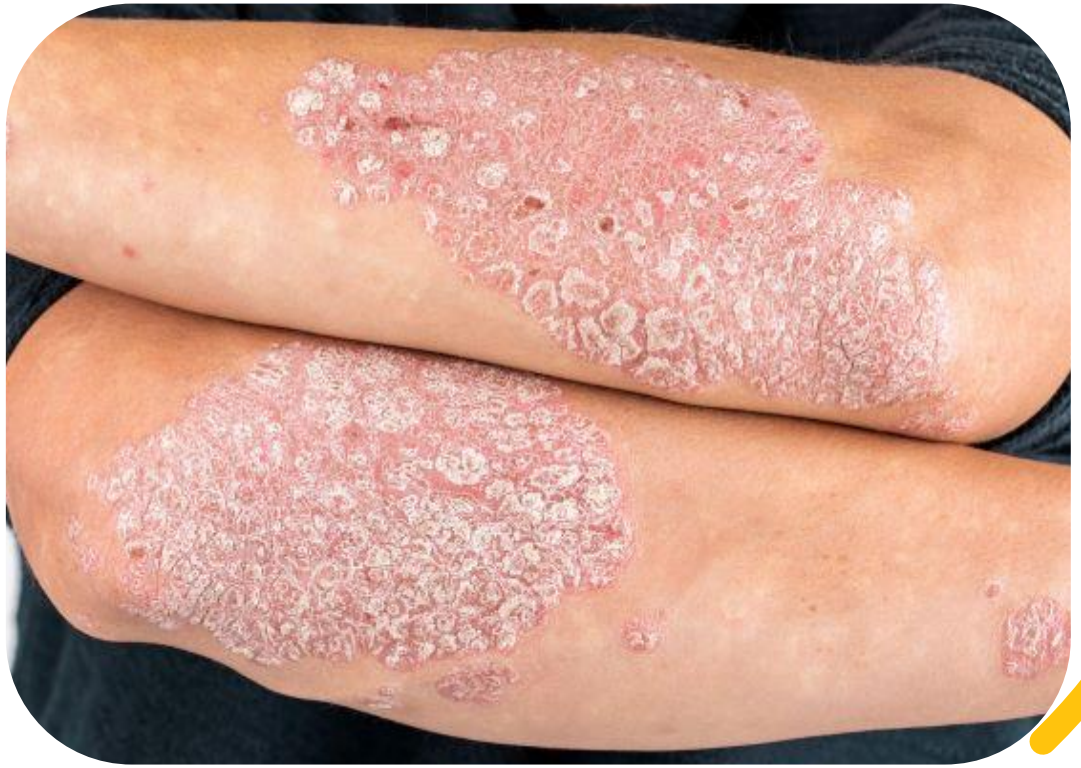






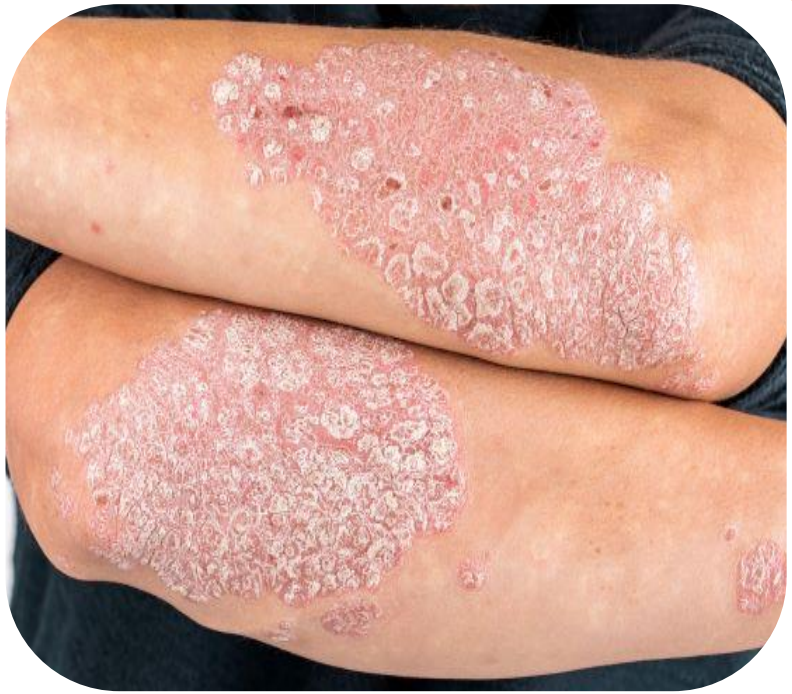
Session 1

- Skin anatomy and physiology
- Psoriasis
- PK PD
- Indications
- Dosage and administration
- Side effects
- Drug Interaction
- **Place in therapy in Dermatology in Psoriasis**



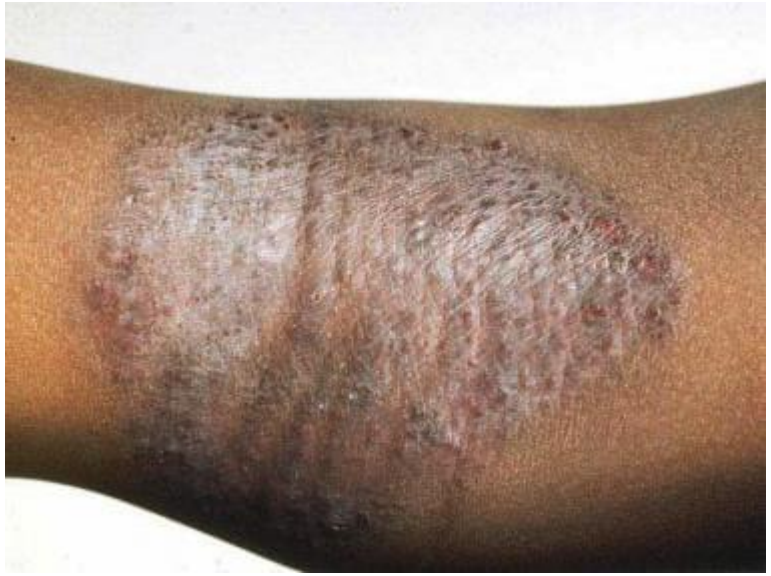
Session 2

- Management of psoriasis
- Clinical Overview of ciclosporin in psoriasis
- Place in therapy in Dermatology in Psoriasis



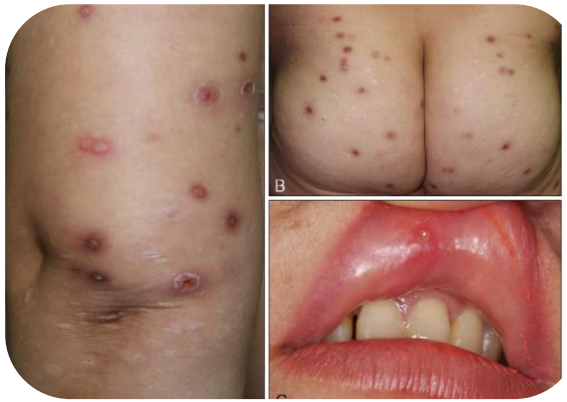
Session 3

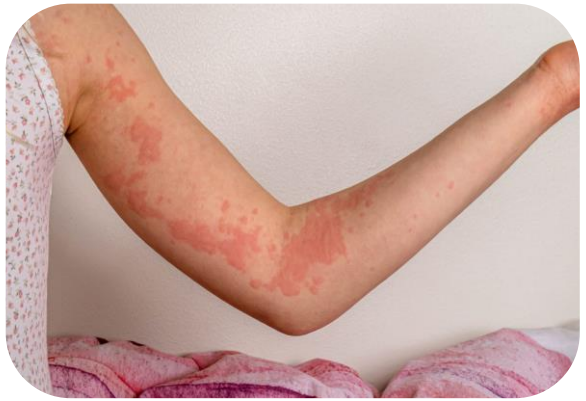
- Skin anatomy and physiology
- Atopic Dermatitis
- Place in therapy in Dermatology in Psoriasis
- Clinical overview

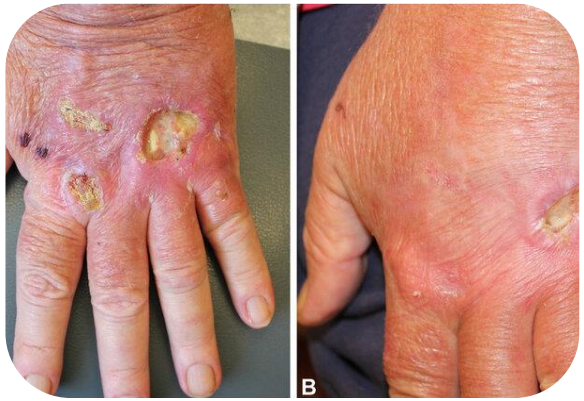


Session 4

- Behcet disease
- Chronic urticaria
- GVHD
- Palmoplantar pustulosis
- Pyoderma gangrenous
- Place in therapy
- Other clinical uses
- Clinical overview



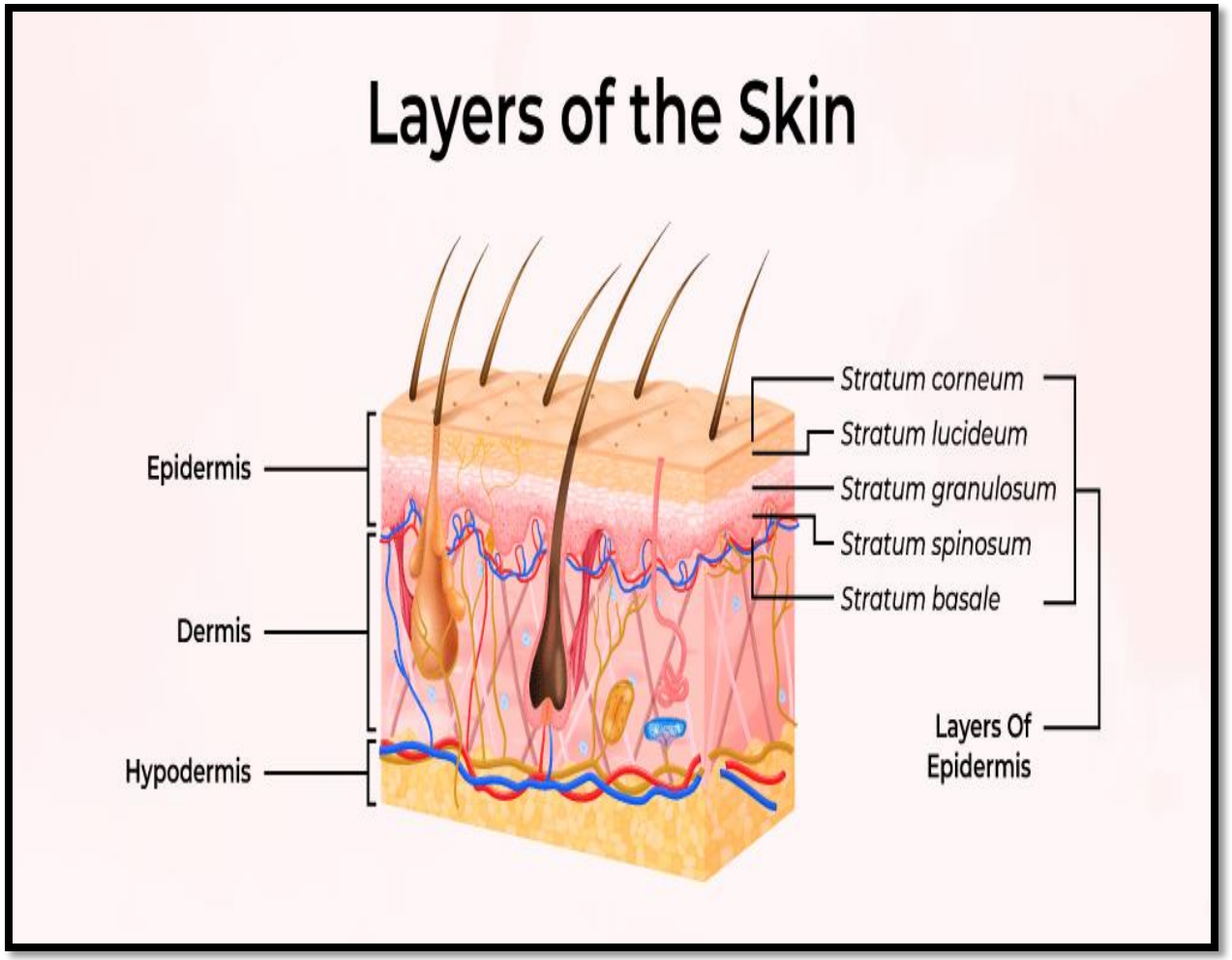




An alternative to biological in Dermatology preferred in Lichen , AD, AA .

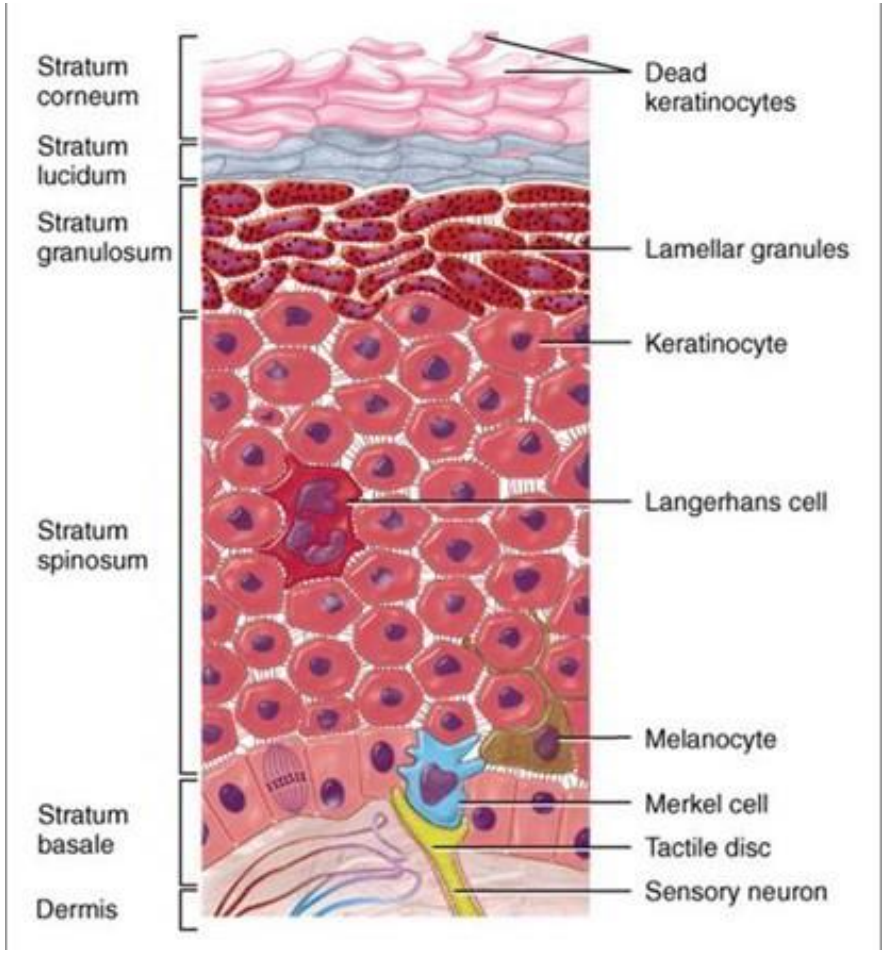
Skin

- Epidermis
  - Waterproof barrier
  - Skin tone
  - 5 layers
- Dermis
  - Hair follicles, blood vessels, lymphatics , sweat gland
  - 2 layers (Papillary and reticular)
- Hypodermis: Fat



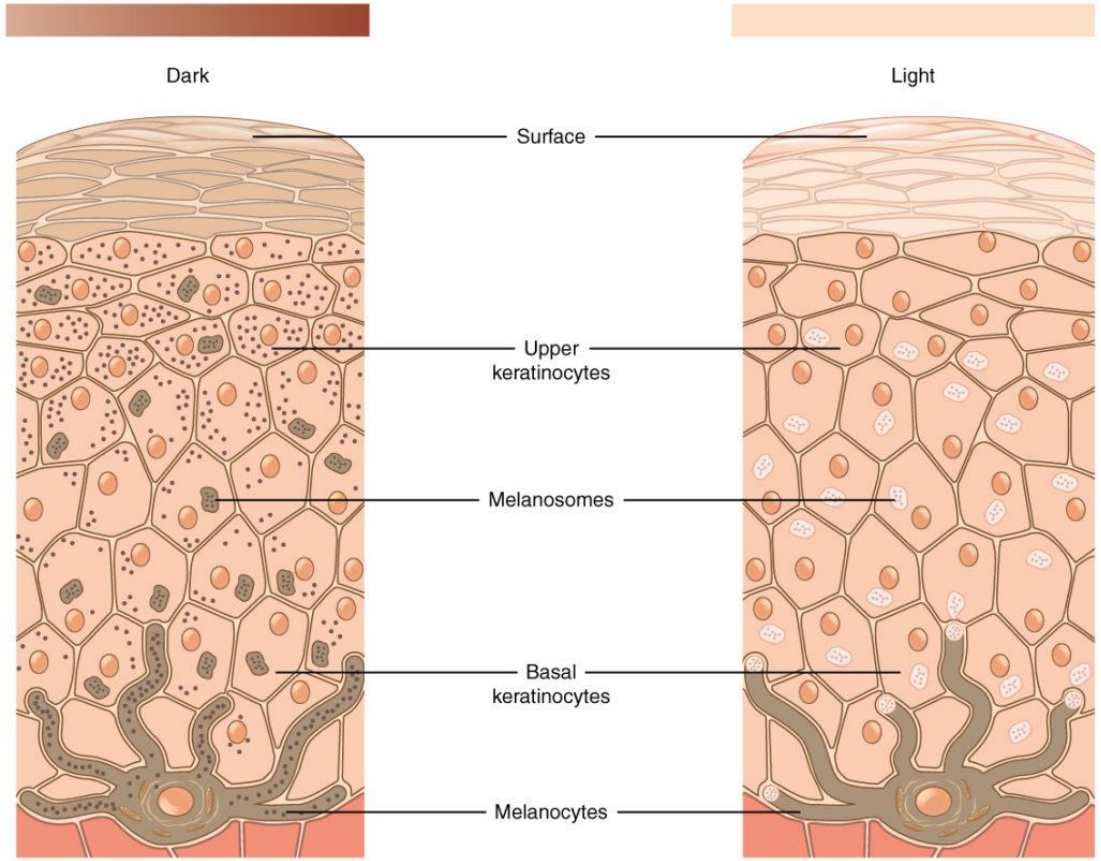
Keratinocytes

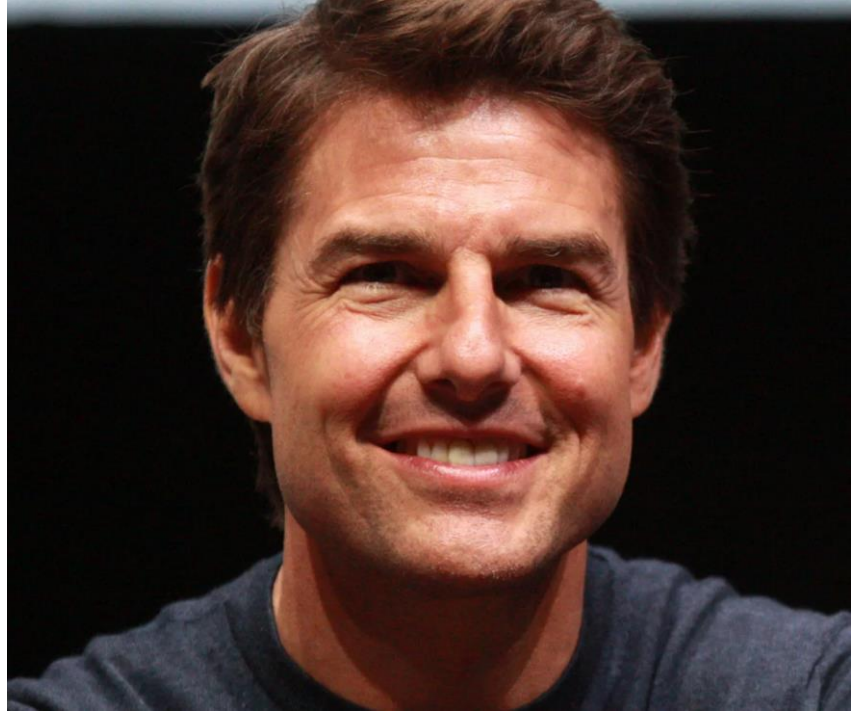
- 90% of epidermal skin cells
- Barrier against environmental damage
- Differentiate from epidermal stem cells
- Migrate towards the surface
- Finally becoming corneocytes
- Shed off every 40 to 56 days



Melanocytes

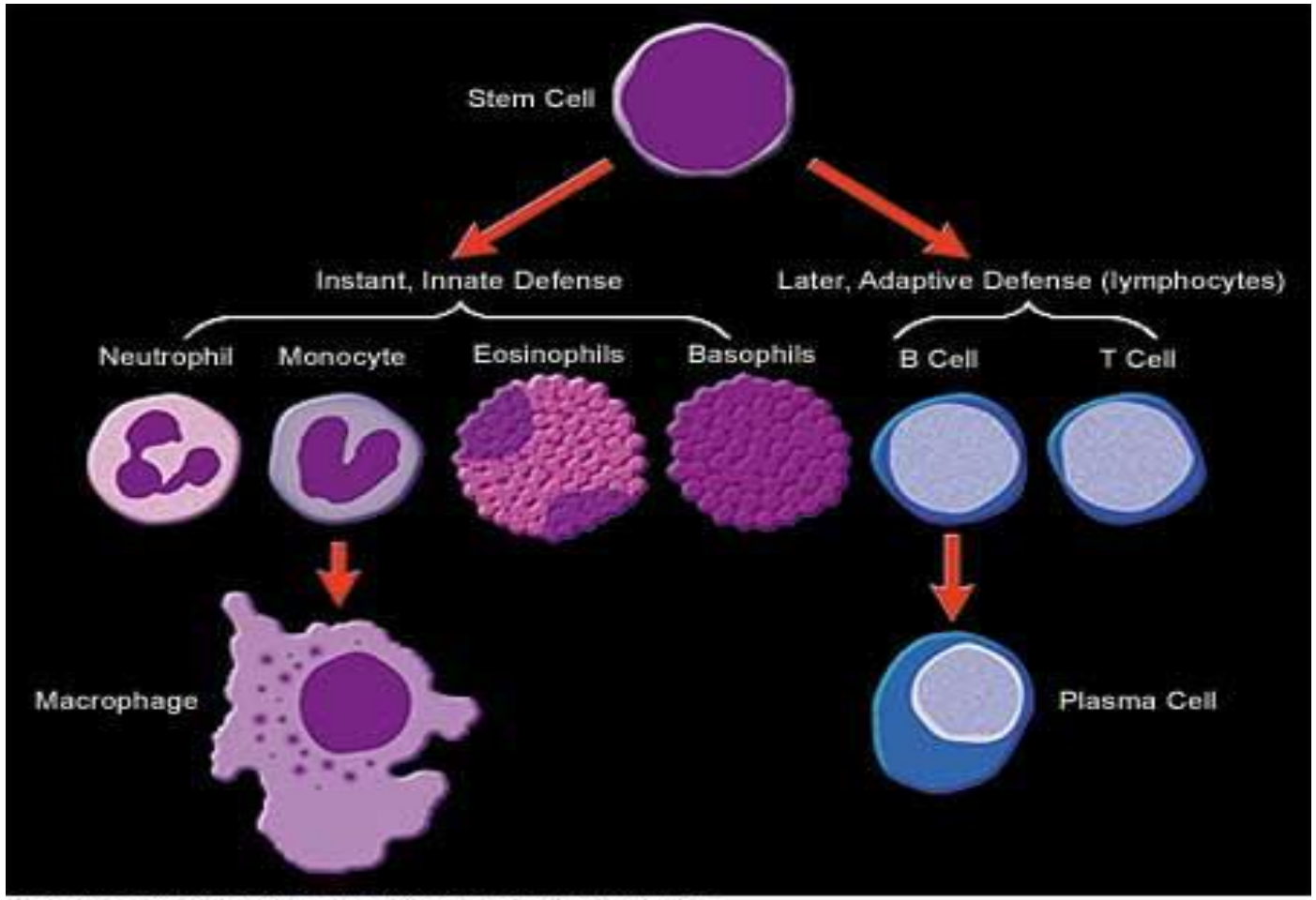
- Melanin-producing
- Dark pigment
- Responsible for skin color
- Contained in melanosomes
- Transported to nearby keratinocytes to induce pigmentation.
- Serves as protection against UV radiation





Immune System



Eade Creative Services, Inc. / George Eade Illustrator

Most important factor in rejection

MHC and APC presents antigen

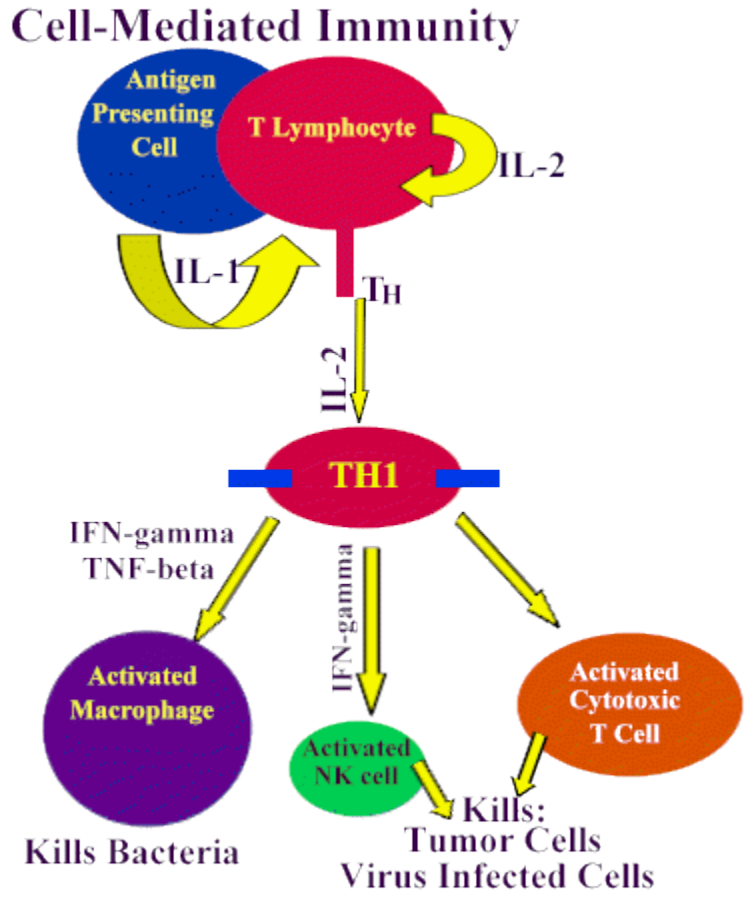
T cell activation

IL2 formation

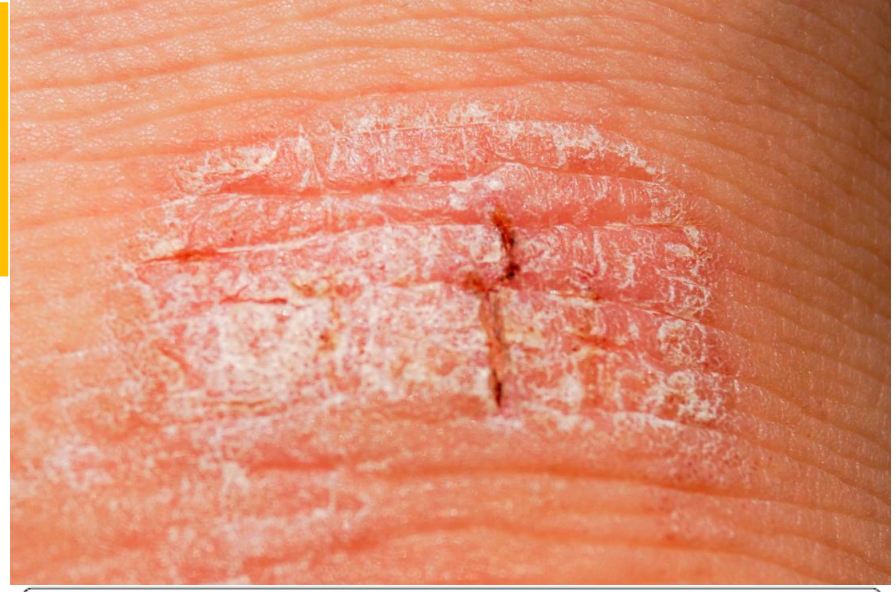
T cell DNA replication

T cell proliferation (CD4 and CD8)

Graft rejection



Plaque psoriasis



- Skin normally replaced in 28-30 days
- Premature keratinocytes replaces skin within 3-5 days
- Premature maturation of keratinocytes induced by an inflammatory cascade in the dermis involving dendritic cells, macrophages, and T cells

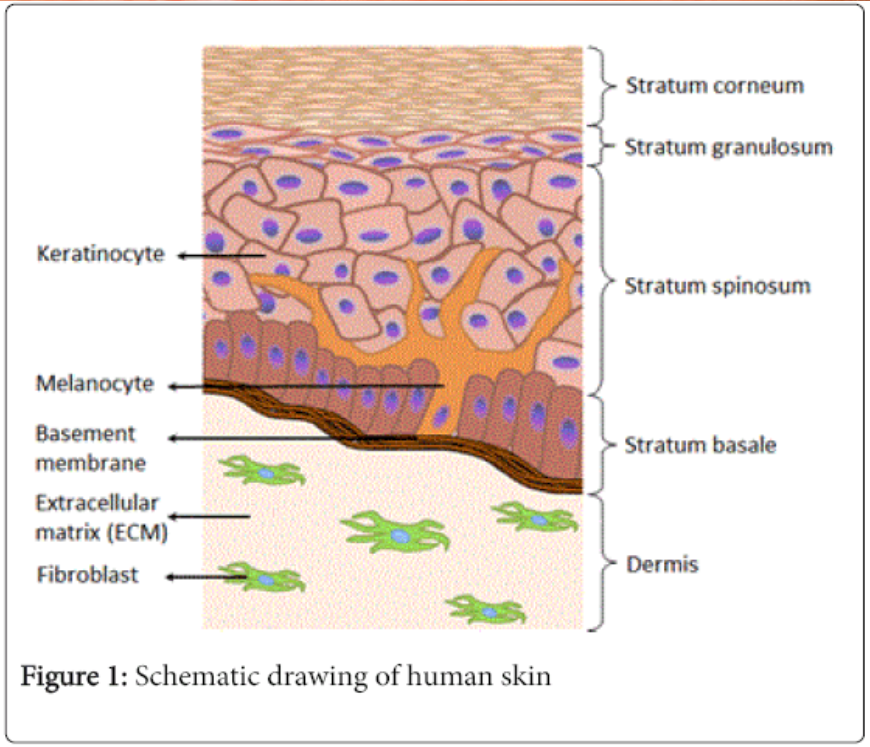
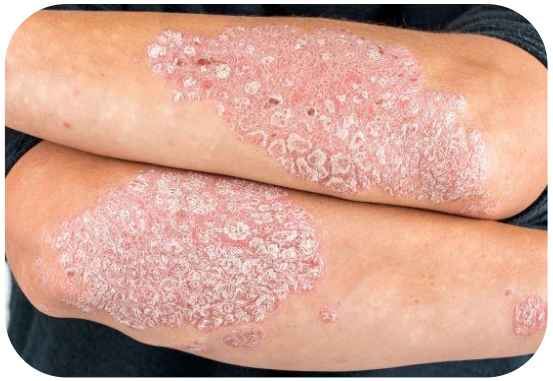
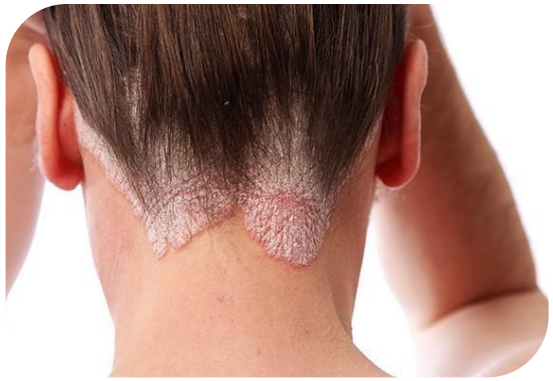


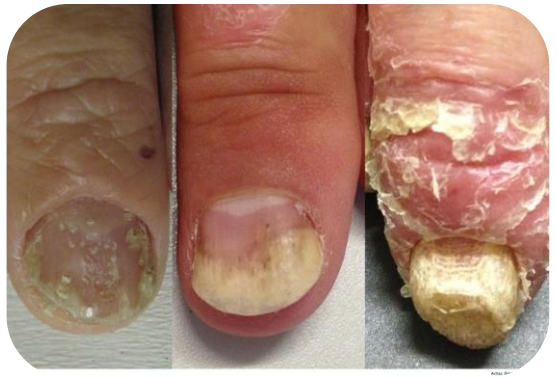
Figure 1: Schematic drawing of human skin



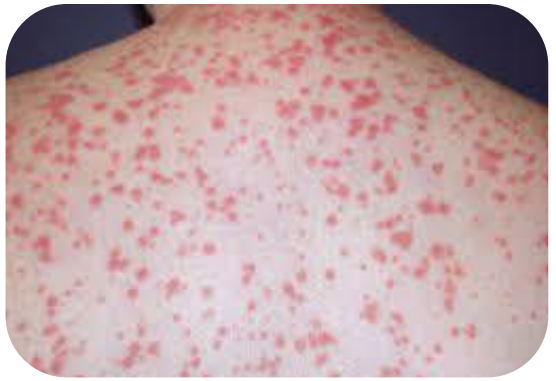
Plaque psoriasis



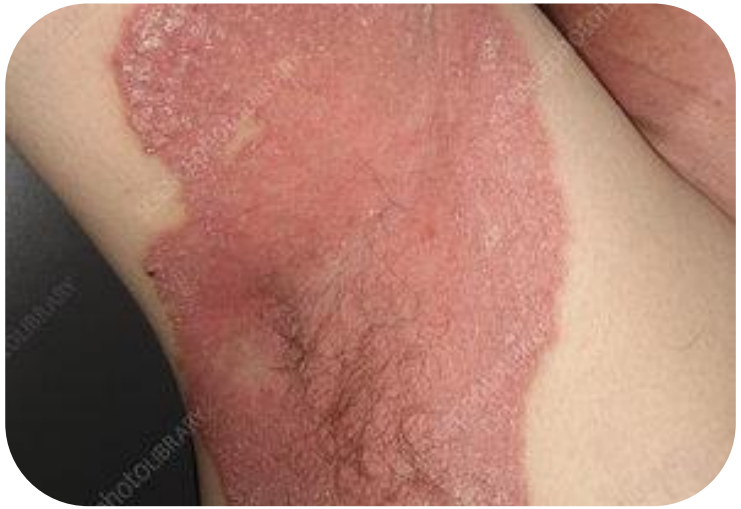
Scalp psoriasis



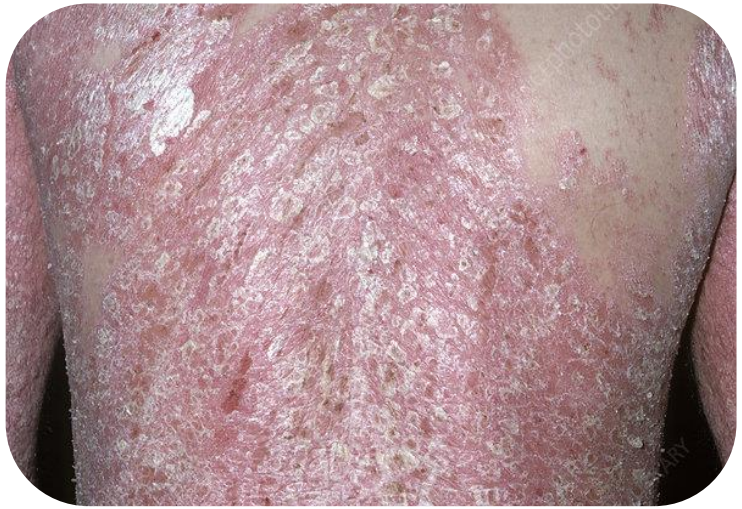
Nail psoriasis



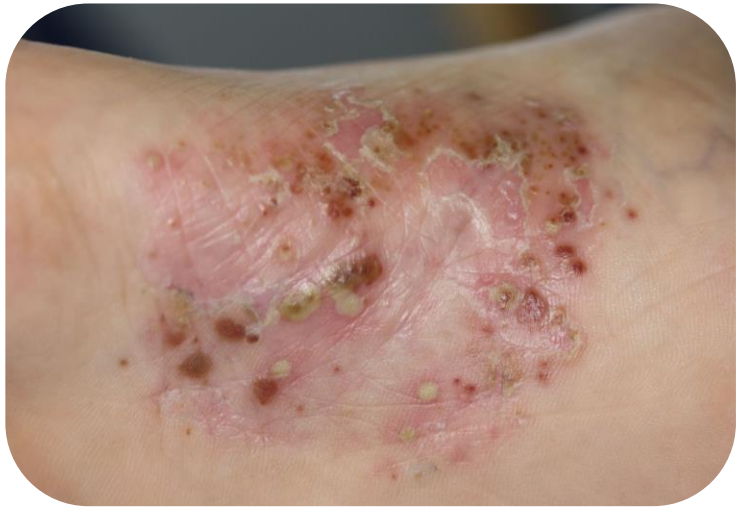
Guttate psoriasis



Inverse psoriasis



Erythrodermic psoriasis



Pustular psoriasis

TYPES OF PSORIASIS

PLAQUE PSORIASIS: 80% OF CASES
Sharply demarcated, red scaly patches of skin with a silvery sheen

SCALP PSORIASIS: 45%-56% OF CASES
Raised red or silver scaly plaques on the scalp, which are often itchy

NAIL PSORIASIS: 50% OF CASES
Fingernails and/or toenails appear dimpled (imagine a golf ball)

GUTTATE PSORIASIS: 10% OF CASES
Skin on arms, legs, and torso is dotted with hundreds of small scaly lesions

INVERSE PSORIASIS: >10% OF CASES
Develops in skin folds like armpits, bellybutton, and more intimate body parts, including the genitals

ERYTHRODERMIC PSORIASIS: 2% OF CASES
Lobster-like redness from head to toe with peeling and scaling; can be extremely dangerous

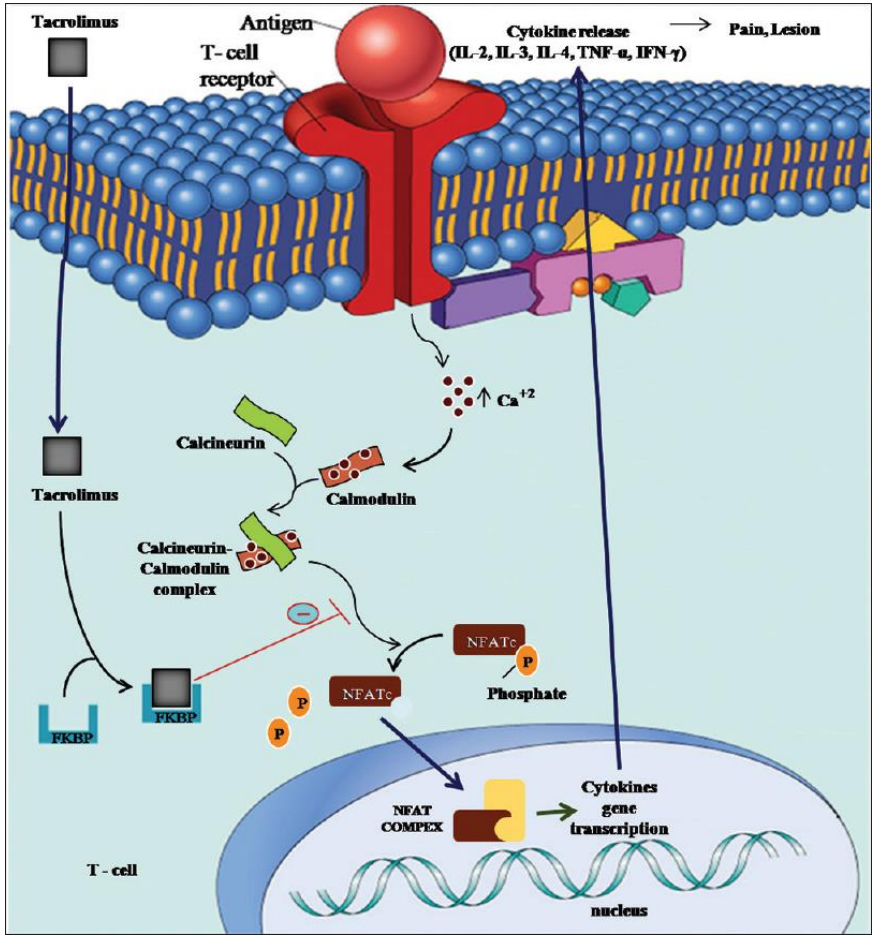
PUSTULAR PSORIASIS: RARE
Dangerous form that covers widespread areas (including hands, feet, and torso) with pus-filled bumps

MOA

- Anti-mycotic agent
- Isolated from a soil fungus
- 1970: Immunosuppressant , anti rejection use in organ transplant
- Disease-modifying Antirheumatic Drugs (DMARDs)
- Immunosuppressive Agent

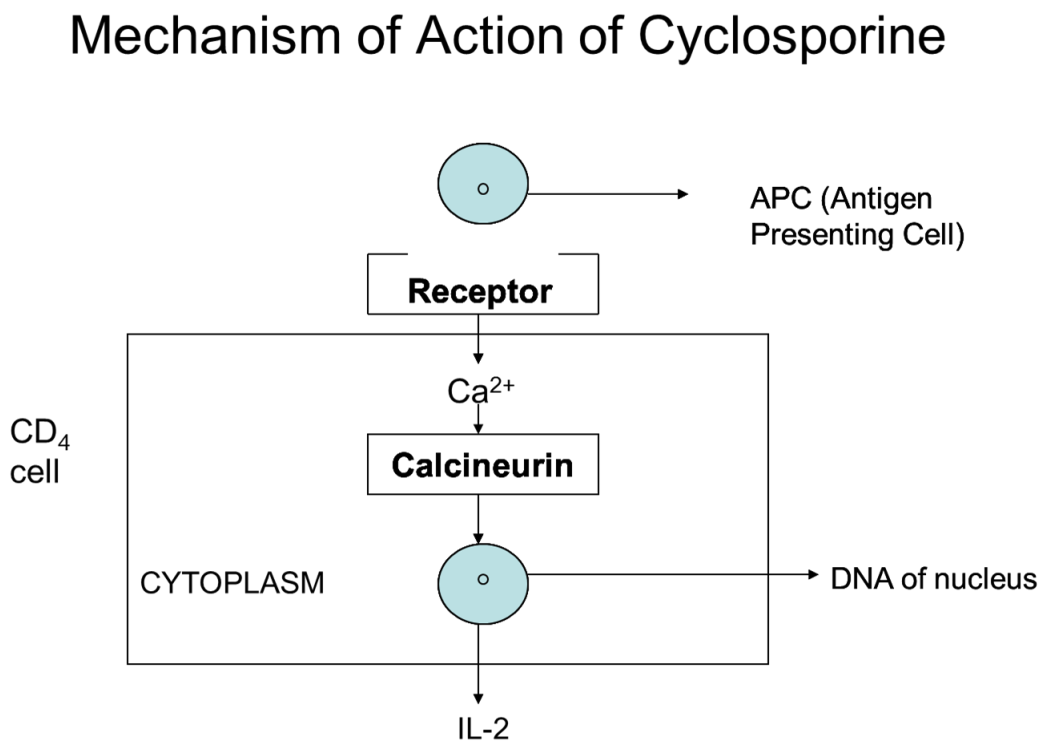
MOA

- Forms active complex of CyA+ Cyclophillin in cytoplasm
- Inhibits calcineurin , a phosphatase which stimulates nuclear factor of activated T cells (NF-AT)
- NF-AT stimulates proinflammatory cytokines, such as interleukin (IL)-2, IL-2, receptor, IL-4, interferon (IFN)-γ and transforming growth factor-β (TGF-β)
- Inhibition of IL-2 and IL-2 receptor, the two main stimulating pathways involved in T cell activation,



Additional functions

- Inhibit the function of antigen -presenting cells
- Inhibition of the release of mast cell mediators including histamine and prostaglandins
- Inhibition of keratinocyte proliferation and keratinocyte cytokine secretion



Pharmacokinetics

Original oral formulation (Sandimmun®)	Simple solution of the drug in olive oil
	40% bioavailability
Microemulsion formulation (Neoral)	Consistent pharmacokinetics
	Reduced variability in absorption both between and within individuals
	Higher Bioavailability
	10% lower dose required for equivalent efficacy

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Pharmacokinetics

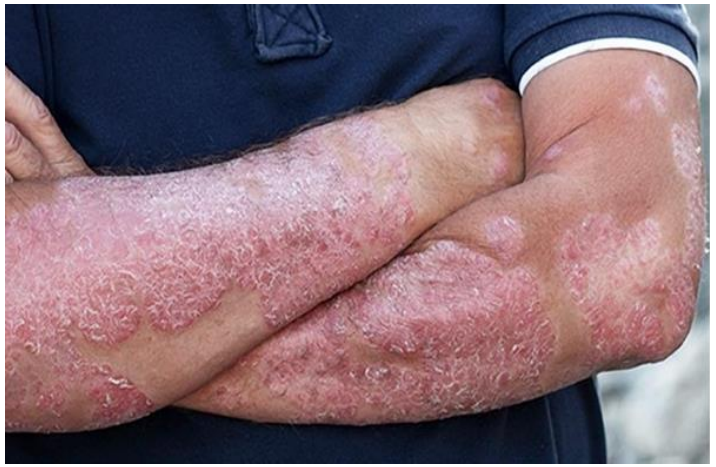
- Therapeutic range :100-300 ng/mL
- Excreted through the bile and faeces and minor proportion through urine (3-6%)
- Terminal half-life of approximately 8.4 hours (range 5 to 18 hours)
- Intrasubject variability of AUC in renal transplant recipients (%CV) : 9% to 21% for Neoral and 19% to 26% for Sandimmune

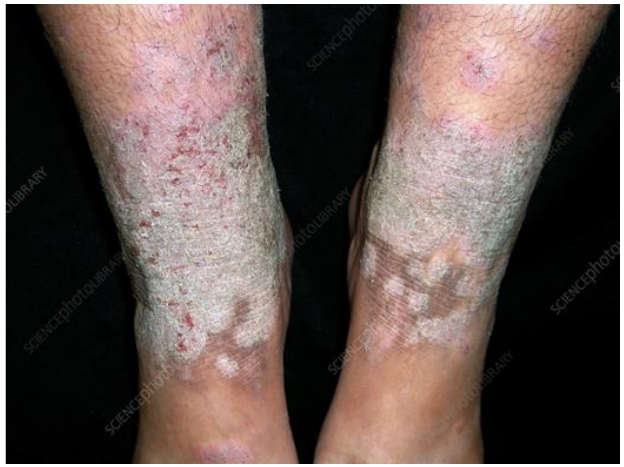
US FDA approved Indications

- Kidney, Liver, And Heart Transplantation
- Rheumatoid Arthritis
- Psoriasis

Dermatology Indication

- Approved
  - Psoriasis
  - AD
- Patients ≥ 16 years old (Children and young people (< 16 years of age most frequently those suffering from AD)





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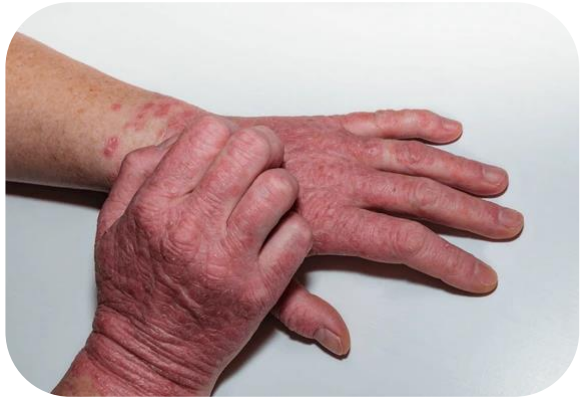
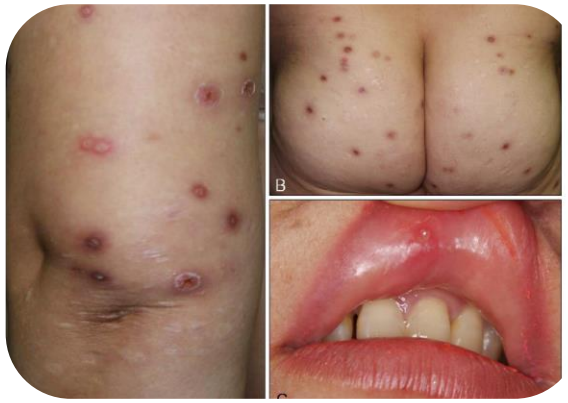
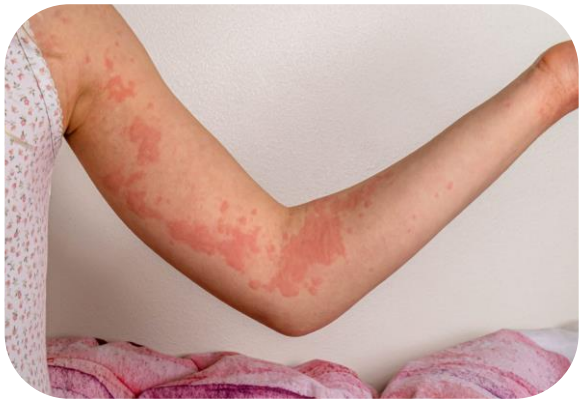
Other clinical uses



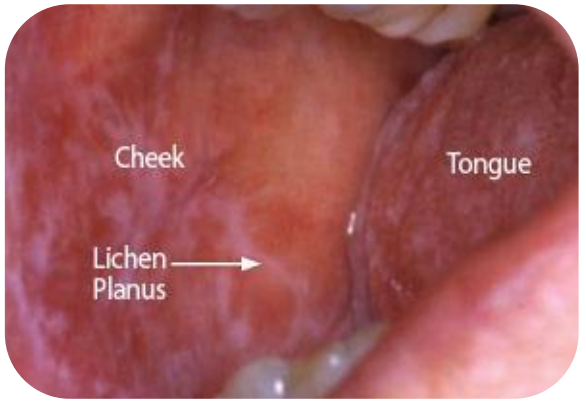
Eczematous dermatoses



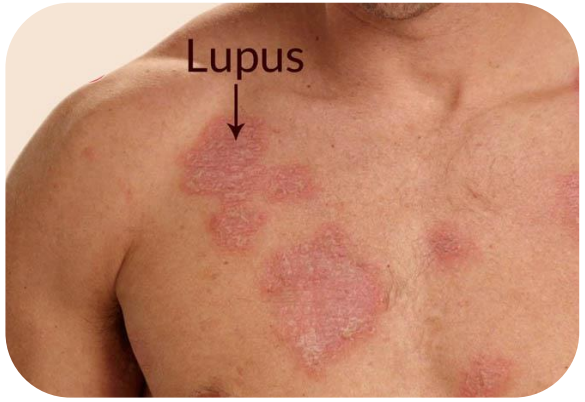
Behçet's disease



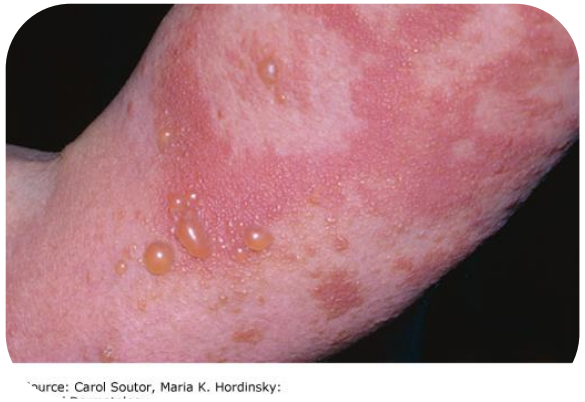
Chronic spontaneous (idiopathic) urticaria,



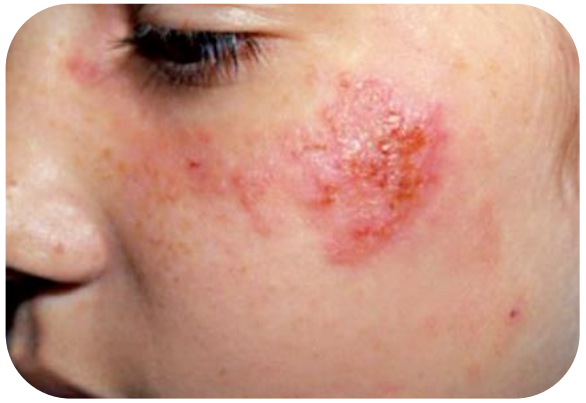
Lichen planus



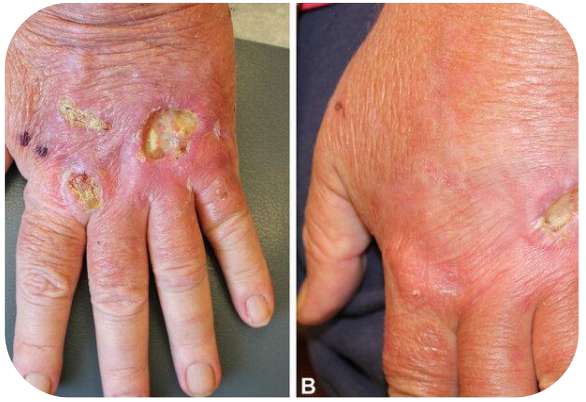
Connective tissue diseases



Immunobullous diseases



Photodermatoses



Pyoderma gangrenosum

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Ciclosporin: Clinical Use and recommendations

British Association of Dermatologists

healthy skin for all

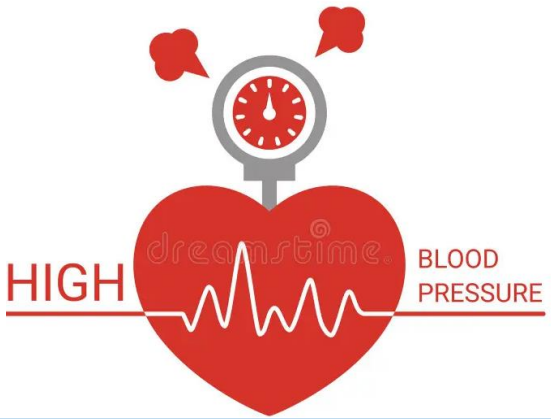
British Association of Dermatologists guidelines for the safe and effective prescribing of oral ciclosporin in dermatology 2018

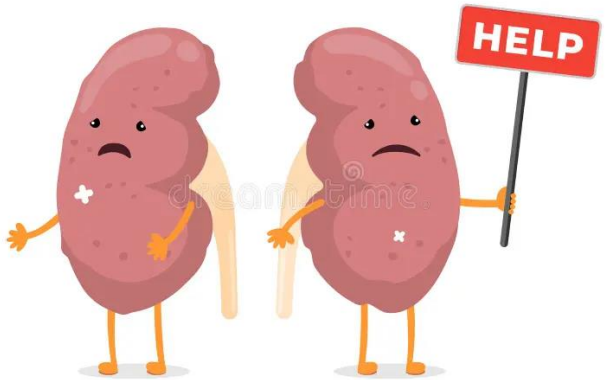
British Association of Dermatologists

healthy skin for all

The most important hazards are **nephrotoxicity** and **hypertension.**

As a result, ciclosporin is **reserved for severe disease** and is generally regarded as a **second line agent**, especially when treatment is likely to be prolonged beyond **2 or 3 months**





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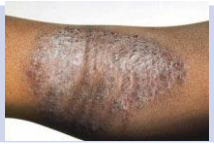
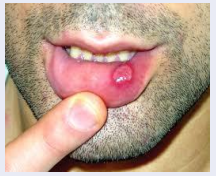
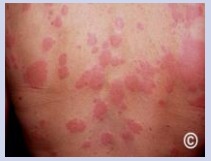
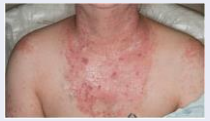
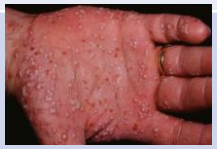
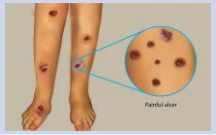
Clinical use	Level of recommendation	Disease features	Photo	Prevalence of disease	Ref
Atopic dermatitis	1+	Eczematous lesions on the flexural areas		3% of overall population	J Allergy Clin Immunol. 2009;124(6):1251–1258.
Behçet's disease	1+	Systemic vasculitis, mucocutaneous manifestations, including recurrent oral and genital ulcerations		13 case/ 1L	Clin Rheumatol. 2007 Apr. 26(4):555-60.
Chronic spontaneous /idiopathic urticaria	1+	presence of urticaria (hives)		1% of overall population	Allergy 2011;66:317–30
Graft versus host disease	1+	erythematous maculopapular rash and oral mucosal lesions		50% in stem cell transplant	Lancet. 2009 May 02;373(9674):1550-61
Palmoplantar pustulosis	1+	appearance of fluid-filled pustules or blisters on the hands and feet.		13 case/ 1L	https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.20087
Psoriasis	1+	Patches of skin become scaly and inflamed, most often on the scalp, elbows, or knees		2.8% of overall population	Indian Dermatol Online J. 2016 Nov-Dec; 7(6): 471–480.
Pyoderma gangrenosum	1+	large, painful sores (ulcers) to develop on skin, most often on your legs		3 to 10 cases per million population	Int Wound J. 2018 Dec; 15(6): 875–879.

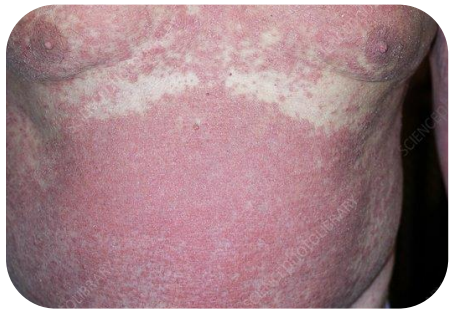
Table X. Strength of recommendation for cyclosporine therapy in psoriasis

Recommendation No.	Recommendation	Strength of recommendation
3.1	Cyclosporine is recommended for patients with severe, recalcitrant psoriasis.	A
3.2	Cyclosporine can be recommended for the treatment of erythrodermic, generalized pustular, and/or palmoplantar psoriasis.	B
3.3	Cyclosporine can be recommended as short-term interventional therapy in patients who flare up while on a pre-existing systemic therapy.	C

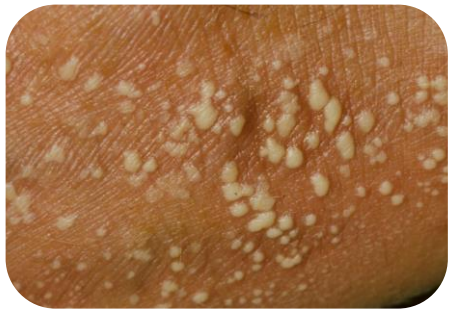
J Am Acad Dermatol. 2020 Jun;82(6):1445-1486.

AAD JAAD Journal of the American Academy of Dermatology

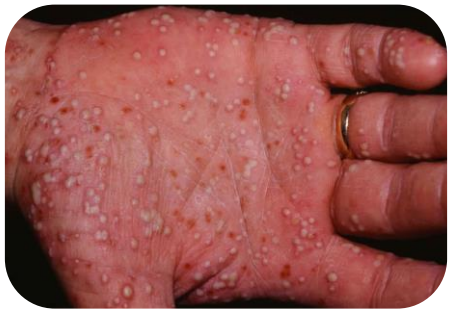
Reported to be effective other types of psoriasis



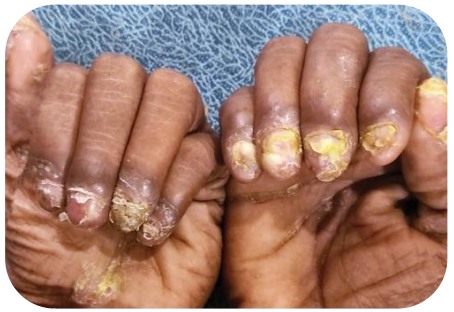
Erythrodermic psoriasis



Generalized pustular psoriasis

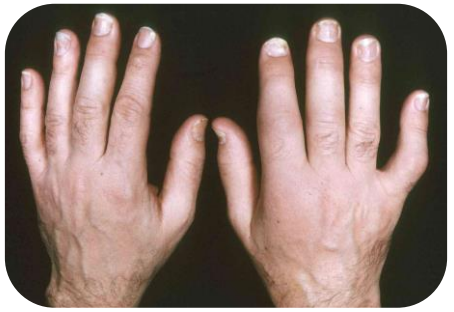


Palmoplantar pustulosis



Acrodermatitis continua of Hallopeau

Psoriatic nail dystrophy



Psoriatic arthropathy

British Association of Dermatologists guidelines for the safe and effective prescribing of oral ciclosporin in dermatology 2018

Standard Regimen

- Inducing remission : 2.5 -5 mg/kg/day ,orally, single dose or two divided doses.
- For rapid control: 5 mg/kg/day
- Discontinue treatment if no response or toxicity within 6 weeks

British Association of Dermatologists guidelines for the safe and effective prescribing of oral ciclosporin in dermatology 2018

Alternative dosing regimens

Intermittent short course

- Reducing cumulative exposure to the drug and potentially renal toxicity

Simplified regimen

- 100 mg/day either as a single dose or divided into two doses of 50 mg, instead of weight-related dosing

Step down regimen 1

- 2.5 mg/kg per day starting dose and an increasing regimen vs 5.0 mg/kg per day starting dose and a decreasing regimen ('step-down regimen') group.
- Higher PASI75 response at 12-week
- Shorter mean time to PASI 50 or PASI 75
- Adverse events similar

J Dermatolog Treat 2007; 18:286-90

Supporting statements for cyclosporine in psoriasis

- Single daily dose = twice-daily dose when the microemulsion formulation is used.
- Post clinical response cyclosporine on 2 consecutive days per week (5 mg/kg/d) may provide benefits
- Weight loss may result in improvement in cyclosporine response

J Am Acad Dermatol. 2020 Jun;82(6):1445-1486

AAD JAAD Journal of the American Academy of Dermatology

Supporting statements for cyclosporine in psoriasis

CI

- Prior PUVA treatment (especially > 200 treatments) or radiation therapy
- Abnormal renal function
- Uncontrolled hypertension
- Malignancy
- Hypersensitivity to cyclosporine
- Live vaccinations should be avoided
- Caution with major infections and poorly controlled diabetes

Baseline monitoring

- History and physical examination BP
- BUN and creatinine
- Urinalysis
- Consider latent tuberculosis test
- LFTs, CBC, lipid profile, magnesium, uric acid, and potassium
- Pregnancy test if indicated

J Am Acad Dermatol. 2020 Jun;82(6):1445-1486

AAD JAAD Journal of the American Academy of Dermatology

Supporting statements for cyclosporine in psoriasis

Ongoing monitoring

- Monitor BP (early morning resting BP), BUN, creatinine every other week during first 3 months and then monthly monitoring if no persistent abnormalities are identified
- Monthly CBC, LFTs, lipid profile, magnesium, uric acid, and potassium
- Pregnancy testing if indicated

J Am Acad Dermatol. 2020 Jun;82(6):1445-1486.

AAD JAAD Journal of the American Academy of Dermatology

Supporting statements for cyclosporine in psoriasis.. Toxicity

- Renal impairment
  - Acute
  - Chronic (increasing glomerular fibrosis with increasing duration of treatment and/or with higher dosages)
- Hypertension
- Malignancies
  - Cutaneous
  - Lymphoproliferative
- Headache, tremor, and paresthesia
- Hypertrichosis
- Gingival hyperplasia
- Worsening acne
- Nausea, vomiting, and diarrhea
- Myalgias
- Flu-like symptoms
- Lethargy
- Hypertriglyceridemia
- Hyperkalemia
- Hyperbilirubinemia d Increased risk of infections
- May increase risk of cancer

J Am Acad Dermatol. 2020 Jun;82(6):1445-1486.

AAD JAAD Journal of the American Academy of Dermatology

Supporting statements for cyclosporine in psoriasis

Pregnancy

- Lower birth weight and shorter duration of pregnancy reported in patients with transplantation; appears not to be teratogenic in patients with transplantation.

J Am Acad Dermatol. 2020 Jun;82(6):1445-1486.

AAD JAAD Journal of the American Academy of Dermatology

Supporting statements for cyclosporine in psoriasis

Nursing

- Cyclosporine contains ethanol and has been found in human breast milk; therefore, ethanol will be orally absorbed by the nursing infant
- A decision should be made whether to discontinue nursing or cyclosporine based on benefit of therapy to the patient.

Fertility

- On the basis of animal studies, there is no effect on fertility

J Am Acad Dermatol. 2020 Jun;82(6):1445-1486.

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Drugs That May Potentiate Renal Dysfunction

Antibiotics	Antineoplastics	Antifungals	Antiinflammatory Drugs	Gastrointestinal Agents	Immunosuppressives	Other Drugs
Ciprofloxacin	Amphotericin B	Amphotericin B	Azapropazon	Cimetidine	Tacrolimus	Fibric acid derivatives (e.g., bezafibrate, fenofibrate)
Gentamicin Tobramycin Trimethoprim with sulfamethoxazole Vancomycin	Ketoconazole	Colchicine Diclofenac Naproxen Sulindac	Ranitidine		Methotrexate	

Drugs That Increase Cyclosporine Concentrations

Calcium Channel Blockers	Antifungals	Antibiotics	Glucocorticoids	Other Drugs
diltiazem nicardipine verapamil	fluconazole itraconazole ketoconazole voriconazole	azithromycin clarithromycin erythromycin quinupristin/ dalfopristin	methylprednisolone	Allopurinol Amiodarone Bromocriptine colchicine danazol imatinib metoclopramide nefazodone oral contraceptives

Drugs/Dietary Supplements That Decrease Cyclosporine Concentrations

Antibiotics	Anticonvulsants	Other Drugs/Dietary Supplements	
nafcillin rifampin	carbamazepine oxcarbazepine phenobarbital phenytoin	bosentan octreotide orlistat sulfinpyrazone terbinafine ticlopidine	St. John's Wort

Take home message

- Keratinocyte : responsible for protecting skin , shed off within 40 days
- Psoriasis : Premature maturation of keratinocytes induced by an inflammatory cascade
- Cyclosporine
  - Class : immunosuppressant and calcineurin inhibitor
  - MOA : Binds to cyclophilin , inhibits calcineurin, deactivate NFAT, Inhibition of IL-2 and IL-2 receptor, T cell deactivation
  - PK : Microemulsion , better bioavailability, less variability (9% vs 19%)
  - Approved indications : Transplant , RA , Psoriasis

Take home message

- Dermatology (1+ recommendations)
  - Approved in Psoriasis and AD
  - Other uses : Eczematous dermatoses, Behçet's disease, Chronic spontaneous (idiopathic) urticaria, Lichen planus, Connective tissue diseases, Immunobullous diseases, Photodermatoses and Pyoderma gangrenosum
- Dose
  - Inducing remission : 2.5 -5 mg/kg/day ,orally, single dose or two divided doses.
  - For rapid control: 5 mg/kg/day
  - Discontinue treatment if no response or toxicity within 6 weeks
- CI : Phototherapy , HTN , CKD, Malignancy
- Monitor BP (early morning resting BP), BUN, creatinine every other week during first 3 months and then monthly
- Side effects : Renal impairment and HTN

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