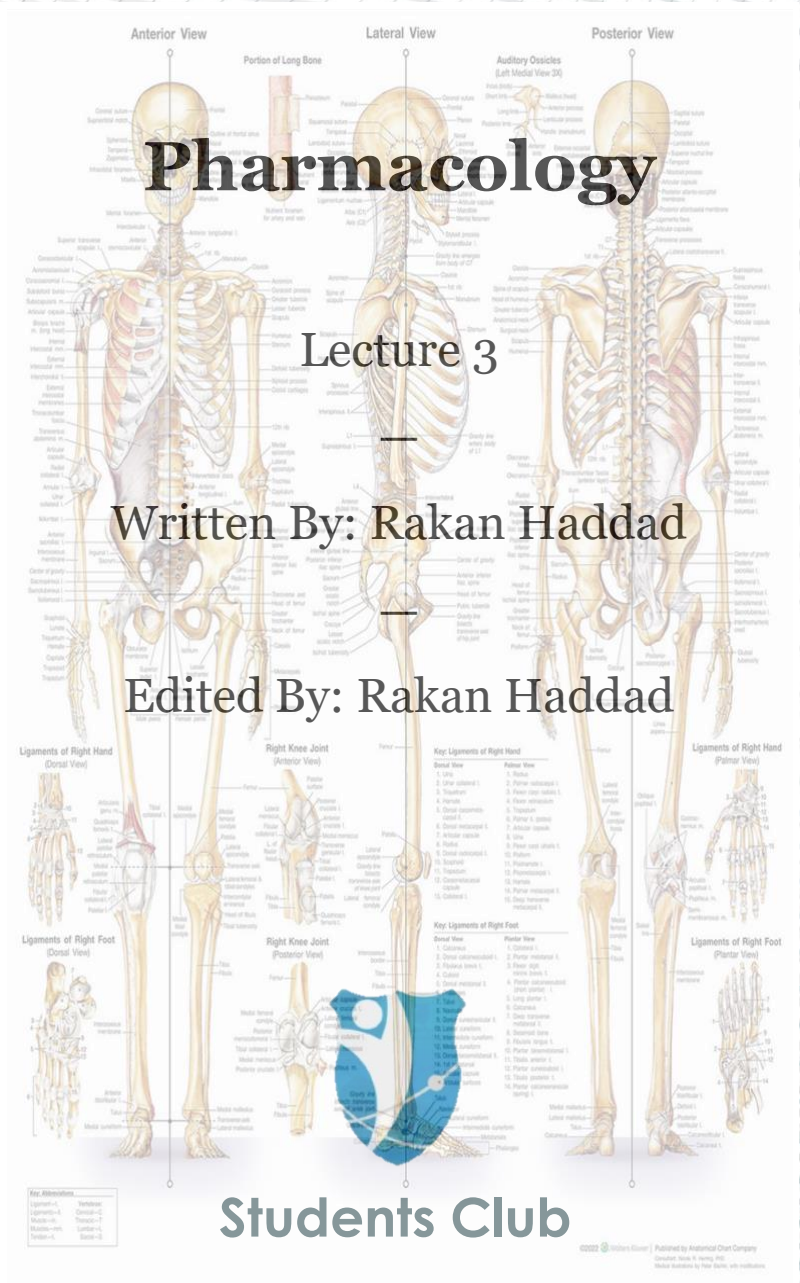
MUSCULOSKELETAL SYSTEM



Pharmacology

Lecture 3

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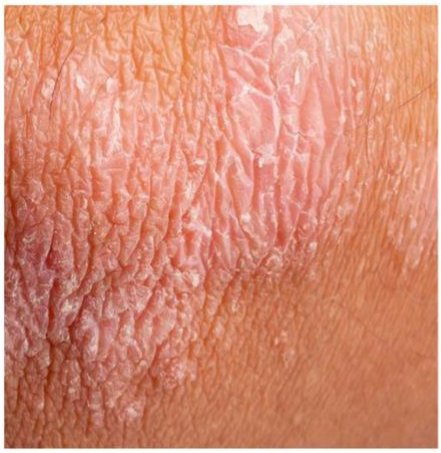
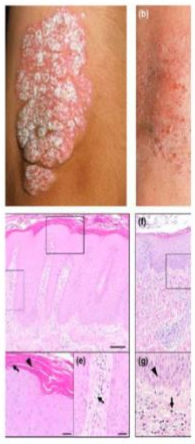
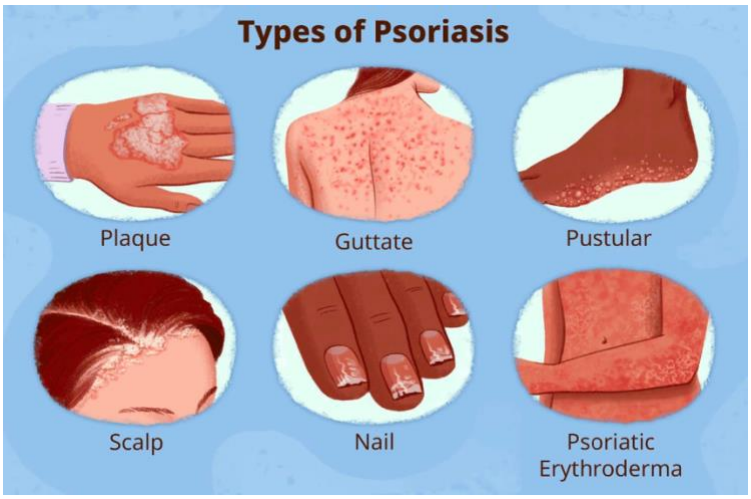
Edited By: Rakan Haddad

Students Club

Psoriasis





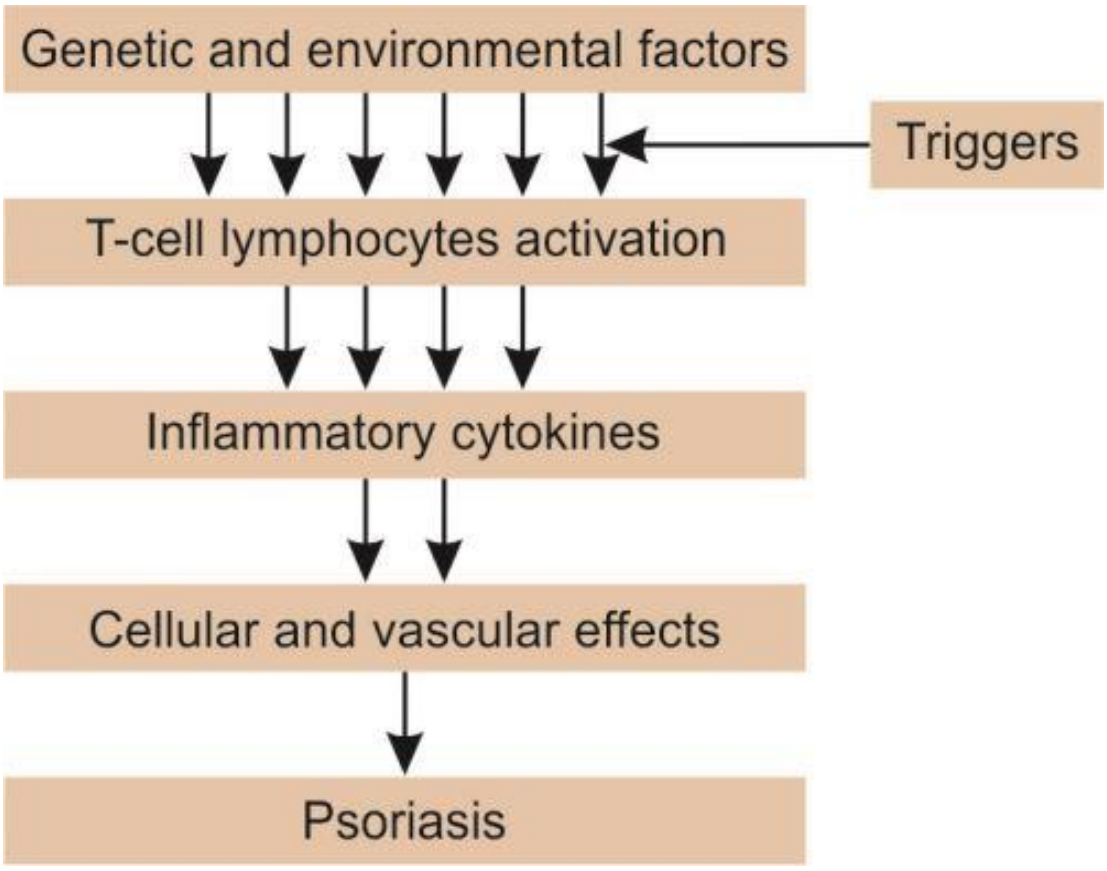


- Soooo… What is this? This is called Psoriasis… It's a chronic inflammatory skin condition in which the skin cells will excessively proliferate (hyoerkeratosis) and inflammed. The name originates as: Psora which means itching & iasis which means a disease.

→The pathophysiology of psoriasis is characterized by an increase in antigen presentation, T-cell activation, and T-helper cell type 1 cytokines (Presentation and activation are mediated by MHC ll, CD40 and CD50 found on the dendritic cells), resulting in thick scaly red plaques due to the bodies response that cuases keratinocyte hyperproliferation and, in some patients, arthritis. Psoriasis is also associated with markers of systemic inflammation, such as increased CRP levels.

- The most common form of psoriasis is plaque psoriasis, which presents as well-demarcated scaly plaques, caused by the hyperproliferation of keratinocytes due to immune dysregulation.
- Guttate psoriasis is usually related to a bacterial infection –specifically streptococcus- with a characteristic pinpoint appearance of lesions.
- Psoriasis is usually localized, but in severe cases, it can trigger a systemic immune response, leading to widespread inflammation and skin lesions across the body. Examples of systemic psoriasis include Pustular Psoriasis and Psoriatic Erythroderma. In such severe cases, systemic immunological intervention is often necessary for effective treatment.

- It may also affect nails, and it is sometimes mistaken for fungal infections due to clinical similarities, meaning that biopsies should be done whenever there is confusion to confirm the diagnosis.
- Psoriasis typically arises from a genetic predisposition and presents in intermittent flare-ups. These flare-ups can be triggered by various factors, including sun exposure, trauma, infections, smoking, and certain medications, such as steroids, beta-blockers, lithium, and antibiotics like amoxicillin.
- However, in rare cases, psoriasis can develop in individuals without a genetic predisposition due to severe environmental or immune-related triggers. Click Me! To watch a short video of psoriasis.



- **Corticosteroids:**
    - They are phospholipase A2 inhibitors making them powerful anti-inflammatory agents.
    - These drugs are the most frequently prescribed medications for treating mild to moderate psoriasis. They are available as oils, ointments, creams, lotions, gels, foams, sprays and shampoos. No need to worry about the different formulations.
    - Mild corticosteroid ointments (hydrocortisone) are usually recommended for sensitive areas, such as the face or skin folds, and for treating widespread patches. Topical corticosteroids might be applied once a day during flares, and on alternate days or weekends during remission.
    - Long-term use or overuse of strong corticosteroids can thin the skin. Over time, topical corticosteroids may stop working.

- **Anti-inflammatory Agents:**
- Topical Corticosteroids:
    - Hydrocortisone→Low potency
    - Prednisolone and Methylprednisolone→Low-Moderate potency
    - Dexamethasone and Betamethasone→Moderate potency
    - Triamcinolone→High potency
    - Fluocinonide→High potency

→ These drugs are used topically to reduce flare-ups and suppress the localized inflammatory response at the site of administration.

→ Triamcinolone may be used as an intra-lesional injection in severe or non-responsive cases to provide targeted anti-inflammatory effects when topical treatments are insufficient.

→ Intra-lesional Triamcinolone injections are the first-line treatment for keloid scars, as they suppress the inflammatory response and prevent further keloid progression. Once the scar is stabilized and reduced in thickness (due to the ability of corticosteroids to inhibit TGF-B which causes a collagen synthesis inhibitory effect), surgical excision may be performed for complete removal, minimizing the risk of recurrence.

- **Topical Cortcosteroids: Adverse Effects:**
  1. Suppression of pituitary-adrenal axis.
  2. Systemic effects because of its immune suppression component making the body more vulnerable to infections.
  3. Skin atrophy due to collagen synthesis inhibitory effect as corticosteroids inhibit fibroblasts from laying down and forming TGF-B.
  4. Erythema→Rebound Vasodilation (Withdrawal Effect). Abrupt discontinuation of some drugs leads to rebound effects (exaggeration of the condition they were used to treat as a result of the upregulatory effect done by the body). Therefore, when these drugs are to be discontinued, tapering of the dose (gradual reduction) rather than sudden withdrawal is recommended.
  5. Pustules.
  6. Acne.
  7. Infections.

  } Due to increased susceptibility for infections

  8. Hypopigmentation→By reverse effects on melanocytes.
  9. Allergic contact dermatitis.

→ **Adverse Effects of prolonged use of topical Corticosteroids:**

- With a long-duration treatment as well as high doses the body will develop tolerance, so if the case wasn't very flared the usage should be intermittent (every other day).

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-One of the side effects that happens to a small percentage of patients is allergic contact dermatitis which is a form of eczema, it might seem contradictory that corticosteroids are used to treat eczema and at the same time can cause it for other patients, but here it's about how corticosteroids are used, in the case of eczema patient these drugs reduces inflammation making them effective for short-term relief of eczema flare-ups, while it can cause eczema-like conditions if the body becomes dependent on them after long high-dosage therapy cessation, as a rebound effect.

-Suppression of pituitary-adrenal axis (a side effect of systemic use), when the body needs to secrete cortisol for its homeostatic effects on glucose levels or in case of stress the pituitary gland secrets ACTH (Adrenocorticotropic hormone) that travels to the adrenal gland commanding it to produce cortisol which is a corticosteroid, and by using these drugs the body starts down-regulating the cortisol production at the adrenal gland and starts being dependent on the exogenous source of cortisol, so in order to cope with this situation physicians should lower the dosage gradually instead of immediate cessation.

- **Vitamin D analogues:**
  - Their action isn't fully understood, but it's speculated that these drugs suppress the expression of CD40, CD80, and MHC2 antigens in dendritic cells.
  - Vitamin D analogues. Synthetic forms of vitamin D — such as calcipotriene and calcitriol can slow skin cell growth.
  - This type of drug may be used alone or with topical corticosteroids.
  - Calcitriol may cause less irritation in sensitive areas.
  - exerts antiproliferative and differentiation- inducing effects in epidermal keratinocytes of lesional psoriatic skin.

- **Drugs for Psoriasis:**

1) Acitretin:
   -Related to isotretinoin. Given orally.
   -Hepatotoxic and teratogenic.
   -Patients should not become pregnant for 3 years after stopping treatment, and also should not donate blood.
   -It has an anti-inflammatory and anti proliferative effects, and is related to the retinoid family (Vit A derivative), it's the last resort if other drugs aren't effective.
2) Tazarotene:
   -Topical.
   -Anti-inflammatory and antiproliferative actions.
   -Teratogenic. Also, can cause burning, stinging, peeling, erythema, and localized edema of skin.
   -From the retinoid family.

- **Calcineurin inhibitors:**

→ Calcineurin is an immune regulator protein related to the Ca+2-calmodulin cascade, as it goes and activates some transcription factors that control the expression of certain genes governing immune related functions leading to immunosuppression and making them useful for patients undergoing organ transplantation.

- Calcineurin inhibitors — such as tacrolimus and pimecrolimus— calm the rash and reduce scaly buildup.
- They can be especially helpful in areas of thin skin, such as around the eyes, where steroid creams or retinoids are irritating or harmful.
- Calcineurin inhibitors aren't recommended in pregnant or breastfeeding.
- This drug is also not intended for long-term use because of a potential increased risk of skin cancer and lymphoma, in addition to a higher susceptibility for infections.

- **Other Topical Drugs:**

  - **Salicylic acid.** Salicylic acid shampoos and scalp solutions reduce the scaling of scalp . May be used alone or with other topical therapy, as it prepares the scalp to absorb the medication more easily→It's anti-inflammatory and keratolytic.
  - **Coal tar.** Coal tar reduces scaling, itching and inflammation. It's available in nonprescription and prescription strengths. It comes in various forms, such as shampoo, cream and oil.
  - These products can irritate the skin. They're also messy, stain clothing and bedding, and can have a strong odor.
  - **Anthralin.** Anthralin is a tar cream that slows skin cell growth. It can also remove scales and make skin smoother.

    →Coal tar & Anthralin are anti-proliferative drugs.

    →Even though these drugs are old, they have no major drawbacks so are still used till this day.

- **New Drugs for Psoriasis**:

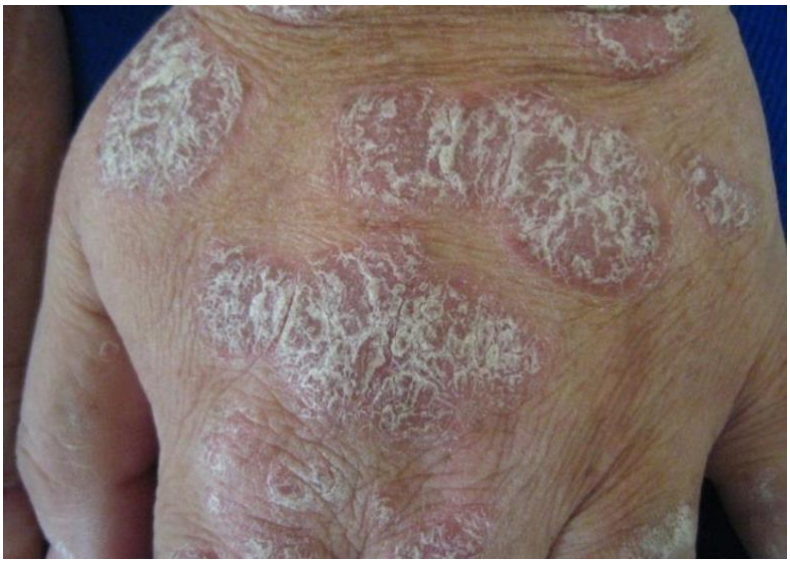
  1) Apremilast (Otezla)
     - psoriasis and psoriatic arthritis.
     - It may also be useful for other immune system-related inflammatory diseases.
     - The drug acts as a selective inhibitor of the enzyme phosphodiesterase 4 (PDE4) and inhibits spontaneous production of TNF-alpha from human rheumatoid synovial cells.

- **Side Effects:**
  1. diarrhea
  2. nausea.
  3. stomach pain.
  4. vomiting.
  5. headache.
  6. sore throat, cough, and fever.
  7. sneezing, runny nose, and nasal congestion.e-to-severe psoriasis demonstrating superior efficacy to apremilast

2) Deucravacitinib (Sotyktu)
   - A new oral treatment option for adults with plaque psoriasis.
   - moderate-to-severe plaque psoriasis
   - It is a once-daily oral medication with its clinical trials in moderate-to-severe psoriasis demonstrating superior efficacy to apremilast
   - MOA: Allosteric inhibitor of tyrosine Kinase 2

- **Side effects**:
  1. Runny nose
  2. Congestion
  3. Sore throat, sore on mouth, lips, gums, tongue or roof of mouth,.
  4. acne.

3) Roflumilast (Zorvye) cream
   - Selective, long-acting inhibitor of the enzyme phosphodiesterase-4 (PDE-4). It has anti-inflammatory effects.
   - Chronic plaque psoriasis
   - An effective topical therapy for use on all psoriasis- affected areas including body, face, and intertriginous areas



4) Tapinarof (Vtama)
   - Tapinarof (Vtama) is a topical (on the skin) medication used to treat plaque psoriasis in adults.
   - MOA: immunemodulation, skin-barrier normalization, and antioxidant activity.
   - It's convenient to use because it's only applied once daily

- Drugs for Psoriasis→ **Biologic Agents:**

  → Etanercept:
  - Dimeric fusion protein of TNF receptor linked to the Fc portion of human IgG_1. IL-13, IL-17, and IL-23 play a role in the pathophysiology of psoriasis.
  - Approved for the treatment of psoriasis, psoriatic arthritis and ankylosing spondylitis in adults

- **Agents affecting Pigmentation:**

1) Trioxsalen.
2) Methoxsalen.

– Are psoralens used for the repigmentation of depigmented macules of vitiligo.

– Must be photoactivated by long-wave-length ultraviolet light (320-400nm) to produce a beneficial effect.

– They intercalate with DNA.

– Can cause cataract and skin cancer.

→ Light therapy might be used for psoriasis.

3) Hydroquinone.
4) Monobenzone.
   -Monobenzone may be toxic to melanocytes resulting in permanent depigmentation.

5) Mequinol

– Reduce hyperpigmentation of skin by inhibiting the enzyme tyrosinase which will interfere with biosynthesis of melanin.