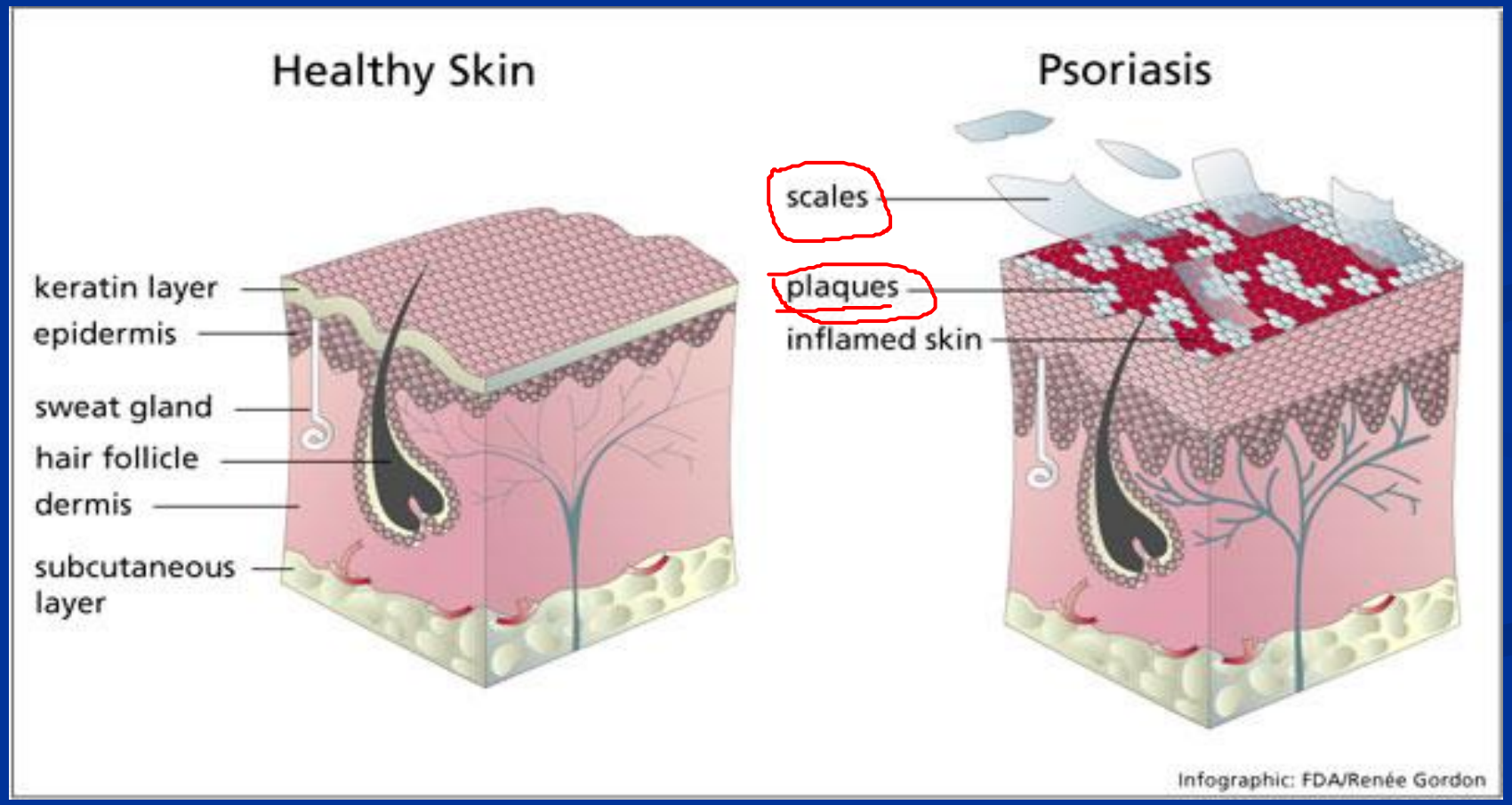
Drugs in psoriasis

A chronic skin condition, immune mediated dermal inflammation consists of painful reddened papules that form plaques with distinct borders. Other patches appear as silvery yellow-white scales

Usually located in elbows, scalp, knees, feet and genitalia

- Psoriasis is an inflammatory skin disease in which skin cells replicate at an extremely rapid rate. New skin cells are produced about eight times faster than normal--over several days instead of a month--but the rate at which old cells slough off is unchanged. This causes cells to build up on the skin's surface, forming thick patches, or plaques, of red sores (lesions) covered with flaky, silvery-white dead skin cells (scales).



hypotheses

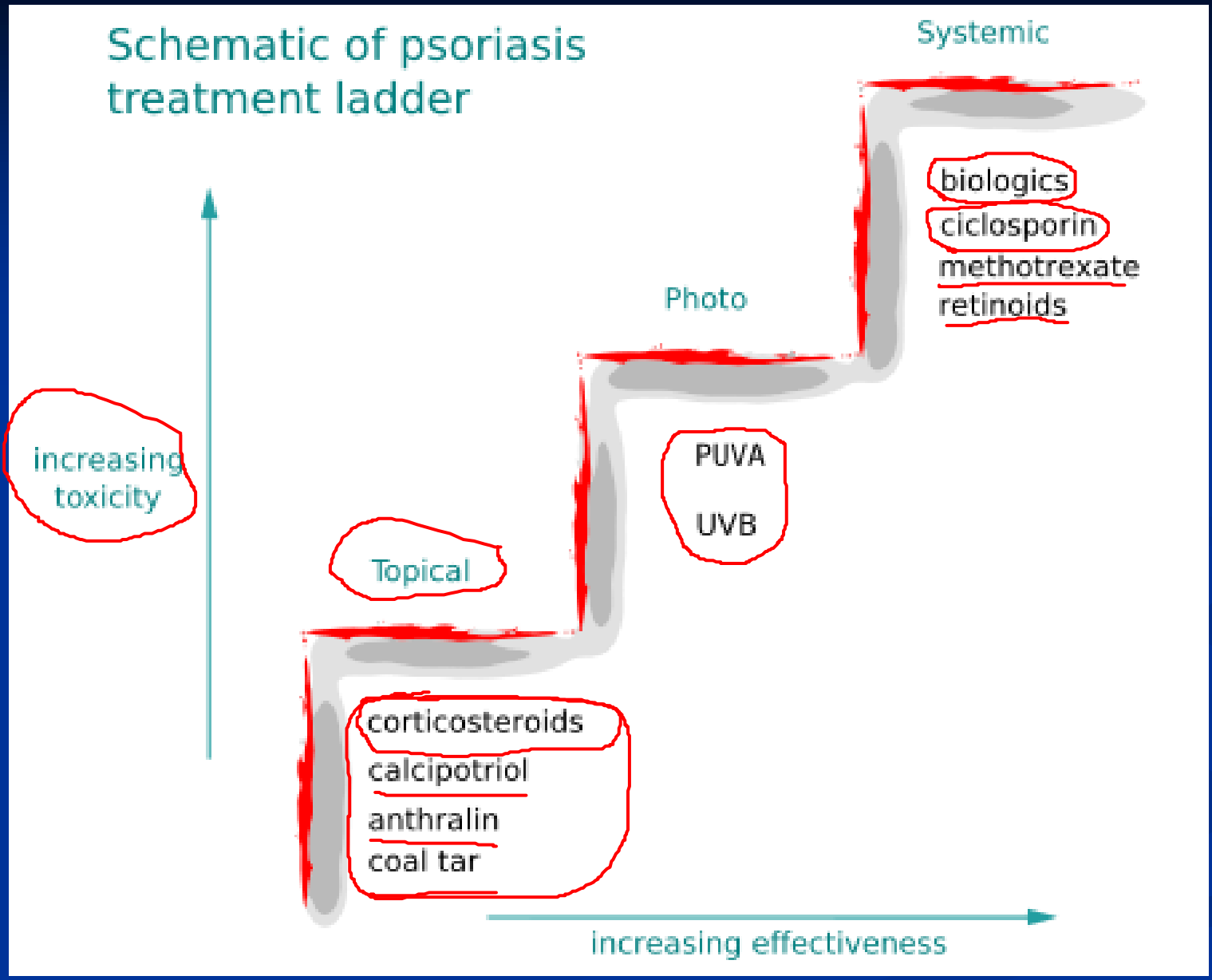
- The first considers psoriasis as primarily a disorder of excessive growth and reproduction of skin cells. The problem is simply seen as a fault of the epidermis and its keratinocytes.

- The second hypothesis sees the disease as being an immune-mediated disorder in which the excessive reproduction of skin cells is secondary to factors produced by the immune system. T cells (which normally help protect the body against infection) become active, migrate to the dermis and trigger the release of cytokines (tumor necrosis factor-alpha TNFα, in particular) which cause inflammation and the rapid production of skin cells. It is not known what initiates the activation of the T cells.
- The immune-mediated model of psoriasis has been supported by the observation that immunosuppressant medications can clear psoriasis plaques.

Treatment options

- As a first step, medicated ointments or creams are applied to the skin. If topical treatment fails to achieve the desired goal then the next step would be to expose the skin to ultraviolet (UV) radiation. This type of treatment is called phototherapy.

- The third step involves the use of medications which are taken internally by pill or injection : systemic treatment.
- Over time, psoriasis can become resistant to a specific therapy. Treatments may be periodically changed to prevent resistance developing and to reduce the chance of adverse reactions occurring: treatment rotation.


Schematic of psoriasis treatment ladder
Systemic
biologics
ciclosporin
methotrexate
retinoids
Photo
PUVA
UVB
Topical
corticosteroids
calcipotriol
anthralin
coal tar
increasing toxicity
increasing effectiveness

Topical CS

- Anti-inflammatory, immunosuppressive
- Quick onset than coal tar and dithranol
- Tachyphylaxis can occur
- High potent agents used in severe cases, thick plaques
- AE local and systemic
- Should not be stopped abruptly – rebound psoriasis

Calcipotriene

- Derivative of vitamin D, acts by slowing down the growth of skin cells
- Used topically (cream; solution) in the treatment of psoriasis
- Safe for long-term application

Coal tar ointment

- Relieves itching, irritation, redness, dryness, scaling caused by psoriasis, seborrhea, or eczema
- It is a keratolytic works by slowing bacterial growth and loosening and softening scales

Dithranol

- May restore normal epidermal proliferation and keratinization
- Useful in thick plaque psoriasis
- Commonly used with SA
- 2 treatment approach: long contact and short contact
- Stains clothes, irritating to normal skin

Tazarotene (cream, gel, or foam)

- It is a retinoid prodrug which is converted to its active form, the cognate carboxylic acid of tazarotene

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Binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ, and RARγ but shows relative selectivity for β, and γ and may modify gene expression

- Has anti-inflammatory and antiproliferative actions

- Teratogenic and can cause burning, stinging, peeling, erythema, and localized edema of skin

UV light

- Patients with psoriasis noticed an improvement in their skin after exposure to sunshine

- Of the many different UV rays emitted by the sun, only UVA and UVB are helpful to people with psoriasis

- Ultraviolet light reduces inflammation in the skin, that's why it can be effective for psoriasis and other inflammatory skin conditions

PUVA (Psoralens + UVA)

- Psoralens include Psoralen; Methoxsalen & Trioxsalen, which are furocoumarins, can be used both topically and systemically

- Psoralens increase sensitivity to solar radiation (given first and followed by UV)

- Methoxsalen has the best oral bioavailability, undergoes less first pass effect and most effective

- Effective in psoriasis, eczema, vitiligo, mycosis fungoides and cutaneous T-cell lymphoma

PUVA MOA

- Inhibit DNA replication
- Decrease in DNA-dependant proliferation
- Alteration of the immune system, suppress T lymphocytes and epidermal Langerhans cells
- Inhibit mast cell release of inflammatory mediators
- Photoactivation stimulates melanocytes and induce their proliferation → promotion of melanogenesis

- **PUVA side effects** include: Nausea, blistering, painful erythema, squamous cell carcinoma, malignant melanoma (extensive PUVA therapy >15 years), cataract (patient should use UVA absorbing eye glasses)

Acitretin

Related to isotretinoin

Given orally for severe pustular psoriasis, good effect

Normalizes desregulated keratinocytes and has antiinflammatory action. Does not suppress sebum

Accumulates in fat → prolonged elimination $t_{½}$ (> 3 months after chronic use)

Hepatotoxic and teratogenic

Acitretin

Adverse effects to Acitretin are similar to other retinoids

More teratogenic than other retinoids

Should not be used in pregnant ladies or those who might get pregnant while on the drug or any time after at least 3 years of discontinuation of therapy and also should not donate blood

Immunomodulators

-Cyclosporin, methotrexate commonly used

-In 2005, the US Food and Drug Administration (FDA) issued an alert about a possible link between topical tacrolimus and pimecrolimus and cases of lymphoma and skin cancer in children and adults [54], and in 2006 placed a "black box" warning on the prescribing information for these medications [55].

Apremilast

oral phosphodiesterase 4 inhibitor,

for the treatment of moderate to severe plaque psoriasis

Phosphodiesterase 4 inhibition reduces production of multiple cytokines involved in the pathogenesis of psoriasis

side effects of apremilast include nausea, **short-term risk of diarrhea** upper respiratory infection, headache, and weight loss.
Periodic monitoring of weight is recommended

Apremilast escalation

is associated with a short-term risk of diarrhea, especially when treatment is started, occurring in roughly 15 to 20 percent of patients.

Tolerability of apremilast is improved by slowly ramping up the dose when treatment is initiated. The recommended dose titration schedule for adults is as follows:

- Day 1 – 10 mg in morning
- Day 2 – 10 mg in morning and 10 mg in evening
- Day 3 – 10 mg in morning and 20 mg in evening
- Day 4 – 20 mg in morning and 20 mg in evening
- Day 5 – 20 mg in morning and 30 mg in evening
- Day 6 and thereafter – 30 mg twice daily

New biologics for posriosis

Ustekinumab is a human monoclonal antibody that targets IL-12 and IL-23.

Guselkumab is a human immunoglobulin G1 (IgG1) lambda monoclonal antibody that binds to the p19 subunit of IL-23. IL-39 also contains this p19 subunit.

Tildrakizumab is a human immunoglobulin G1 (IgG1) kappa monoclonal antibody that binds to the p19 subunit of IL-23. In 2018, the FDA approved tildrakizumab for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Secukinumab, an anti-IL-17A monoclonal antibody, is an effective treatment for moderate to severe plaque psoriasis

Ixekizumab — In March 2016 the FDA approved ixekizumab, a humanized monoclonal antibody against IL-17A, for the treatment of moderate to severe plaque psoriasis in adults. Phase III trials support the efficacy of ixekizumab

Brodalumab, an anti-IL-17 receptor A monoclonal antibody, has demonstrated high efficacy for psoriasis. In February 2017, the FDA approved brodalumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies