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DERMATOLOGY

Translating Psoriasis Guidelines into Practice: Patient Selection and Comorbidities

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Outline

- General approach to treatment selection

- Specific populations
  - Psoriatic arthritis
  - Cardiovascular comorbidities:
  - History of malignancy
  - Tuberculosis

****Discussion limited to FDA approved therapies**

Classification - International Psoriasis Council (IPC)

Psoriasis classification:

Candidate for topical therapy OR
Candidate for systemic therapy

Candidates for systemic therapy must meet at least 1 of the following criteria:

(1)BSA ≥ 10%
(2)Disease involving special areas (i.e. face, palms, soles, etc.)
(3)Failure of topical therapy

Strober B et al. JAAD 2020 Jan;82(1):117-122.

Topical Therapies in Psoriasis

“Proactive Approach” in Topical Treatment

- Reactive versus proactive treatment approach
- Treat areas that frequently flare but are now **clinically quiescent**
- **Twice-weekly treatment** of these areas as ”proactive treatment” to prevent flares
- **”Mix-and-match”:** Many topical agents can be used for proactive treatment, including steroidal and non-steroidal options

Elmets CA et al., Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. J Am Acad Dermatol. 2021 Feb;84(2):432-470. doi: 10.1016/j.jaad.2020.07.087. Epub 2020 Jul 30. PMID: 32738429.

Methotrexate: In Whom Do I Use It?

- Lack health insurance
- Medicare patients without significant comorbidities
- Pediatric psoriasis
- Psoriatic arthritis (but little effect on enthesitis or dactylitis)
- Combined with a biologic or phototherapy

Methotrexate Contraindications

- **Absolute Contraindication**
  - Pregnancy (Do not conceive for at least 3 months following therapy in men and women)
  - Breastfeeding
  - creatinine clearance <50 mL/min

Relative Contraindication

- Alcohol intake (>5 drinks per week)
- Renal disease
- Hepatic disease
- Severe hematologic abnormalities
- Active infections
- Hepatitis B and C infection
- Immunodeficiency

Kalb RE, Strober B, Weinstein G. Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol. 2009 May;60(5):824-37.

Methotrexate: Common side effects

- Nausea and diarrhea
  - 1-5gm of folic acid daily

- Hair loss (temporary and reversible)

3 Biggies: Methotrexate Toxicities

- Hepatotoxicity:
  - Risk Factors: Alcohol; Obesity; Diabetes; hepatotoxic medications; History of liver disease—Hepatitis B or C; Persistent abnormal LFTs; Hyperlipidemia
- Pulmonary fibrosis
- Myelosuppression

Cyclosporine: In Whom Do I use it?

- “Crisis patient”: Erythrodermic psoriasis, severe pustular psoriasis or plaque psoriasis
- Bridge to other long-term therapies such as biologics
- Possibly in pregnant women with severe flare

Cyclosporine

- For severe psoriasis, start CsA at 4-5mg/kg/day divided into BID dosing
- Good efficacy: 70% clear or almost clear in 8-16 weeks at 5mg/kg/day
- Cyclosporine should be tapered, not stopped abruptly.

Cyclosporine Serious Adverse Effects

- **Nephrotoxicity**: interstitial fibrosis and renal tubular atrophy over time
  - Reduction in renal blood flow related to afferent arteriolar vasoconstriction
  - Angiotensin II type I (AT1) receptor antagonist may reduce the nephrotoxicity
- **Hypertension**
- **Malignancy**: skin cancers, lymphoproliferative disorders

Ren Fail. 2004 Sep;26(5):467-77.

Acitretin: In Whom Do I Use It?

- Moderate plaque psoriasis
- Palmoplantar psoriasis
- History of skin cancer
- Combined with phototherapy for synergy

Acitretin: How do I use it?

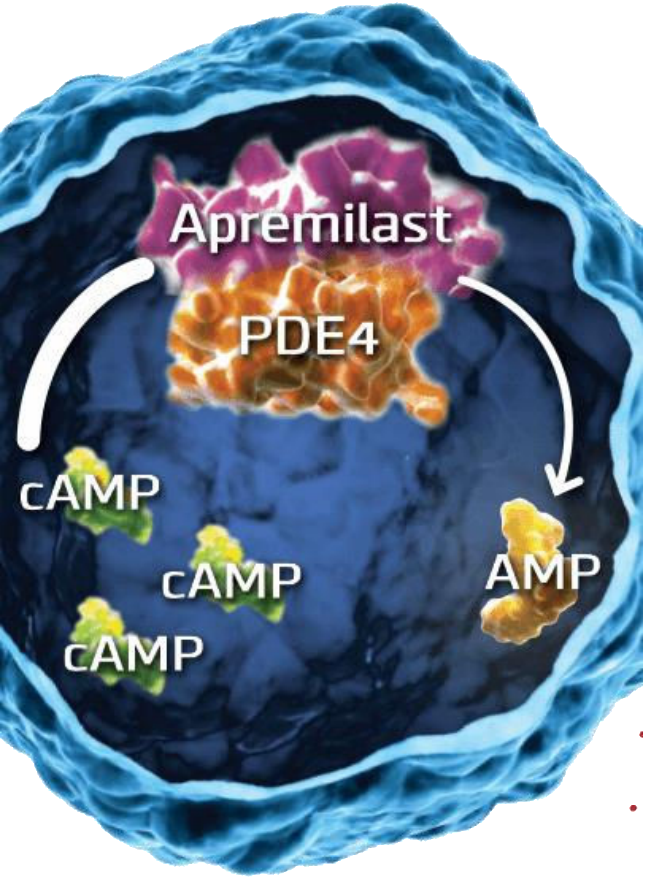
- Range: 10-50 mg/day PO
- Median dose: 25mg/day PO
- Lower doses (≤ 25 mg/d) less effective but minimize side effects
- When acitretin is added to UV, light dose may need to be reduced by 30%-50%

Acitretin Contraindications:

- A potent teratogen and must be avoided in women of childbearing potential
  - Formerly pregnancy category X
  - Contraception required
  - 3-year warning posttreatment to avoid pregnancy
  - Alcohol alters half-life from 49 hours to 120 days
  - [No reproductive risk due to paternal treatment with acitretin.][1]

- Severely impaired liver or kidney function

1. Geiger JM, Walker M. 2002;205(2):105-7. PubMed PMID: 12218221.



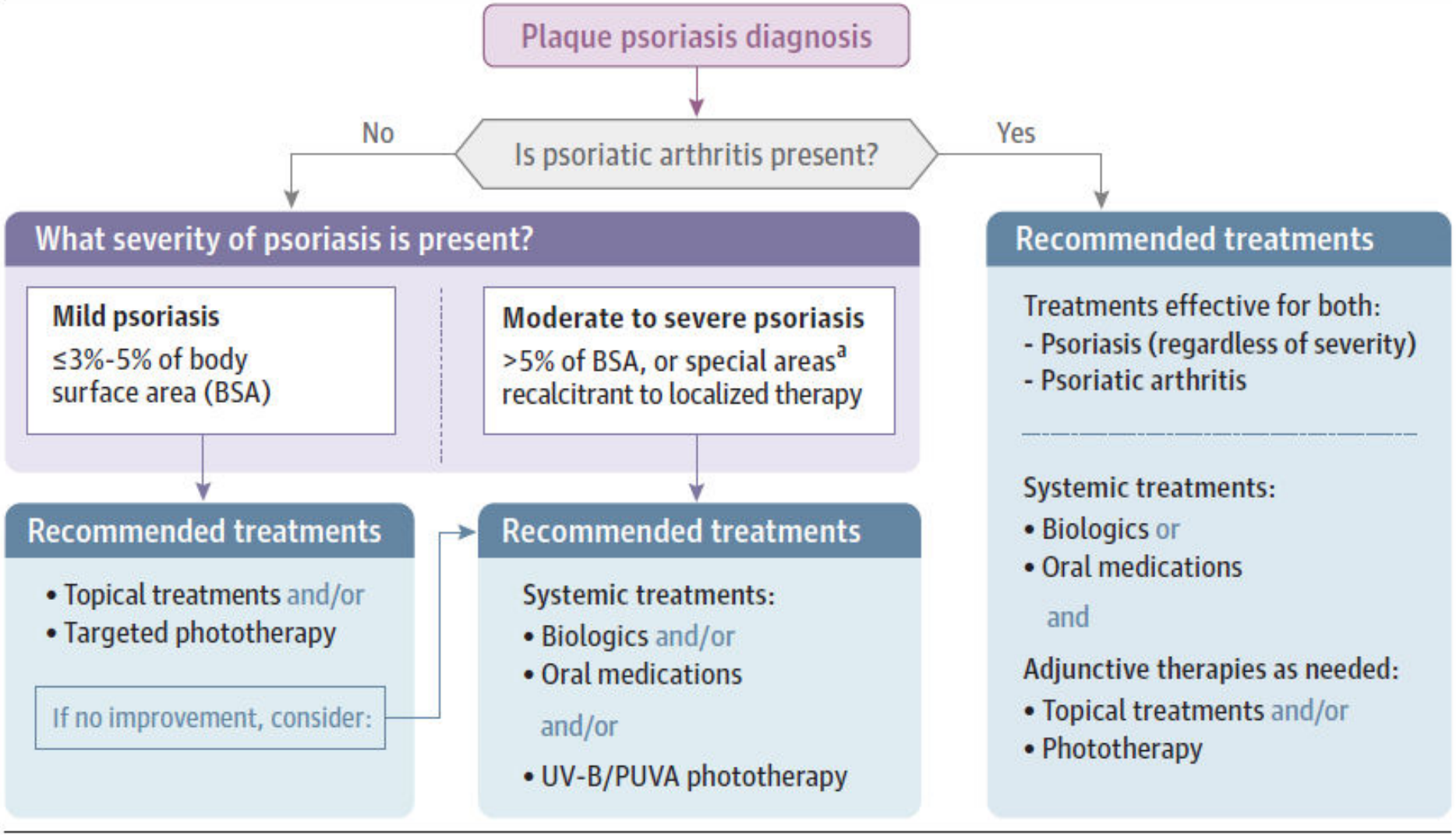
Apremilast

- Phosphodiesterase-4 (PDE4) inhibitor
- Approved for patients with plaque psoriasis who are candidates for phototherapy or systemic therapy **[across all psoriasis severities]; and psoriatic arthritis**
- Dosing: Days 1 through Day 6 dose-escalation from 10mg in AM to 30m BID. 30 mg BID maintenance.
- AEs: **GI Intolerance** (nausea and diarrhea); **Weight decrease:** 5-10% body weight decrease in 6.7% patients
- Renal adjustments necessary for those with severe renal impairment (creatinine clearance < 30 mL per minute)
  - 30 mg once daily

Immunomodulator that *decreases* pro-inflammatory (↓TNF-alpha, IL2, 12, 23) and *increases* anti-inflammatory (↑IL10)
1/3 patients achieve PASI75 by week 16. Diarrhea in some patients upon initiation.

Choosing a biologic?

Overall Treatment Approach for Plaque Psoriasis



[a] Special areas include the scalp, palms, soles, genitalia, and nails.

PUVA indicates psoralen and UV-A.

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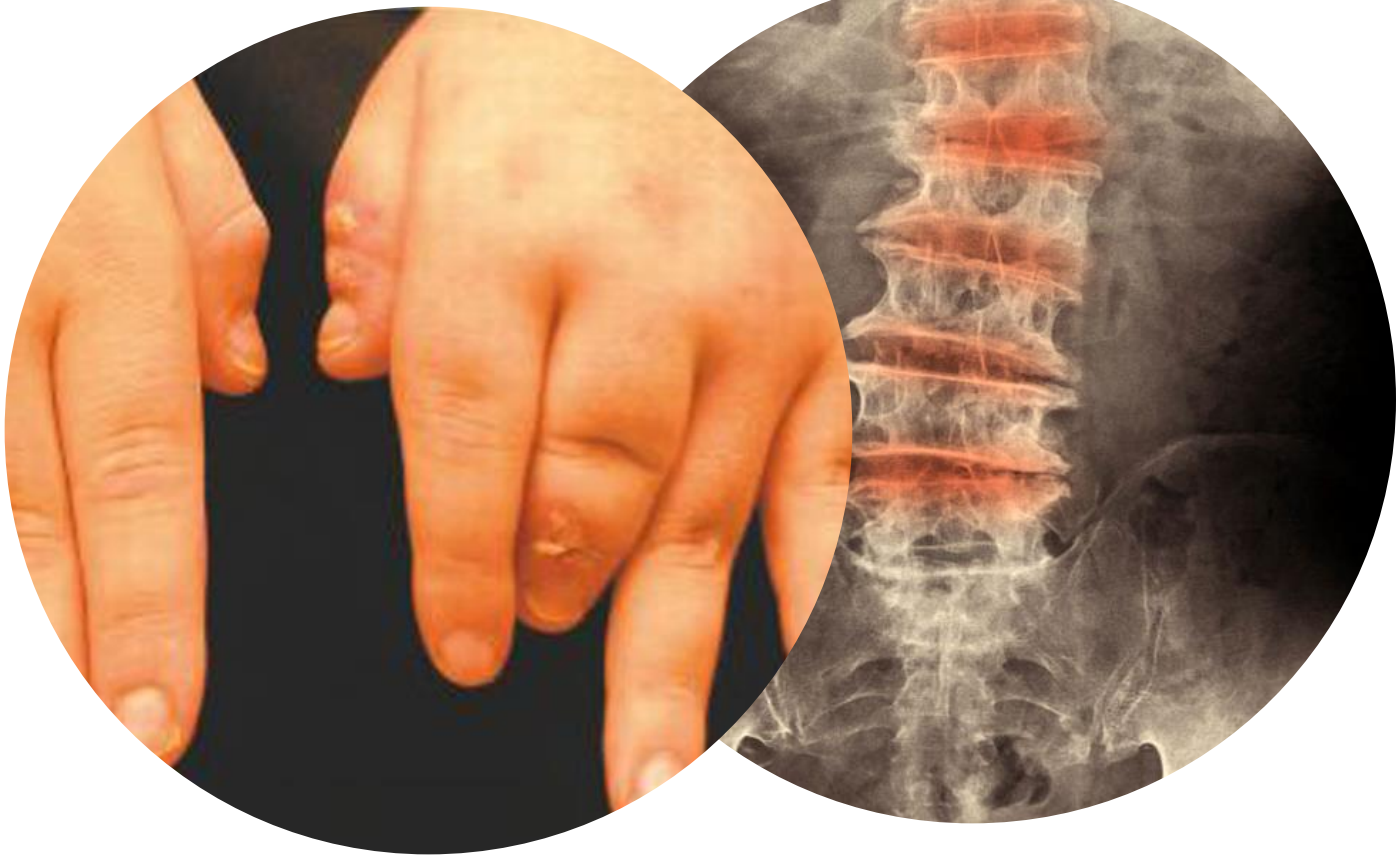
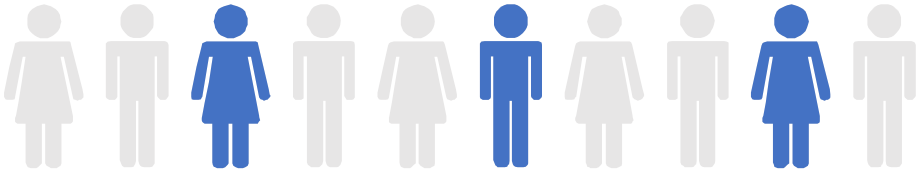
FDA-approved biologics for psoriasis

Drug class	Agent	Indication
TNF antagonists	• Etanercept (Enbrel) • Infliximab (Remicade) • Adalimumab (Humira) • Certolizumab (Cimzia)	Psoriasis, PsA
p40 IL-12/23 antagonist	• Ustekinumab (Stelara)	Psoriasis, PsA
IL-17 antagonists	• Ixekizumab (Taltz)	Psoriasis, PsA
	• Secukinumab (Cosentyx)	Psoriasis, PsA
	• Brodalumab (Siliq)	Psoriasis
IL-23 antagonist	• Guselkumab (Tremfya) • Risankizumab (Skyrizi)	Psoriasis, PsA
	• Tildrakizumab (Ilumya)	Psoriasis

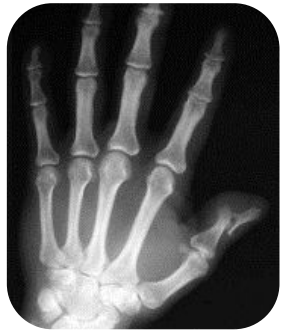
FDA, U.S. Food and Drug Administration; PsA, psoriatic arthritis



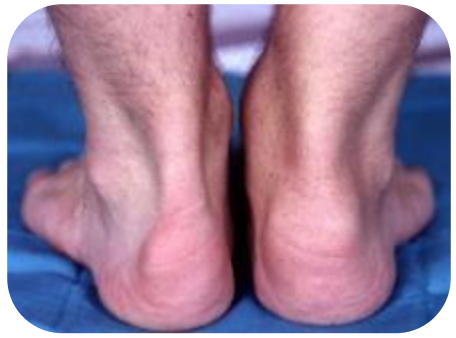
Psoriatic Arthritis



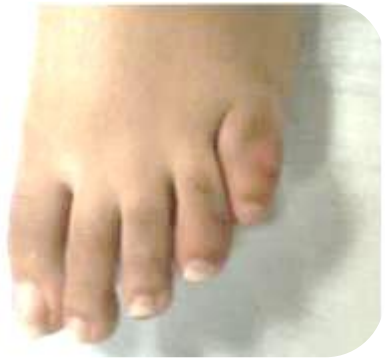
1 in 3 Patients with psoriasis have PsA



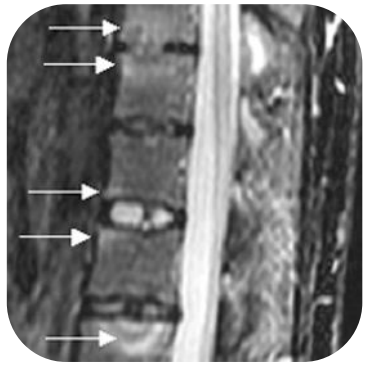
Peripheral arthritis



Enthesitis



Dactylitis



Axial spondylitis

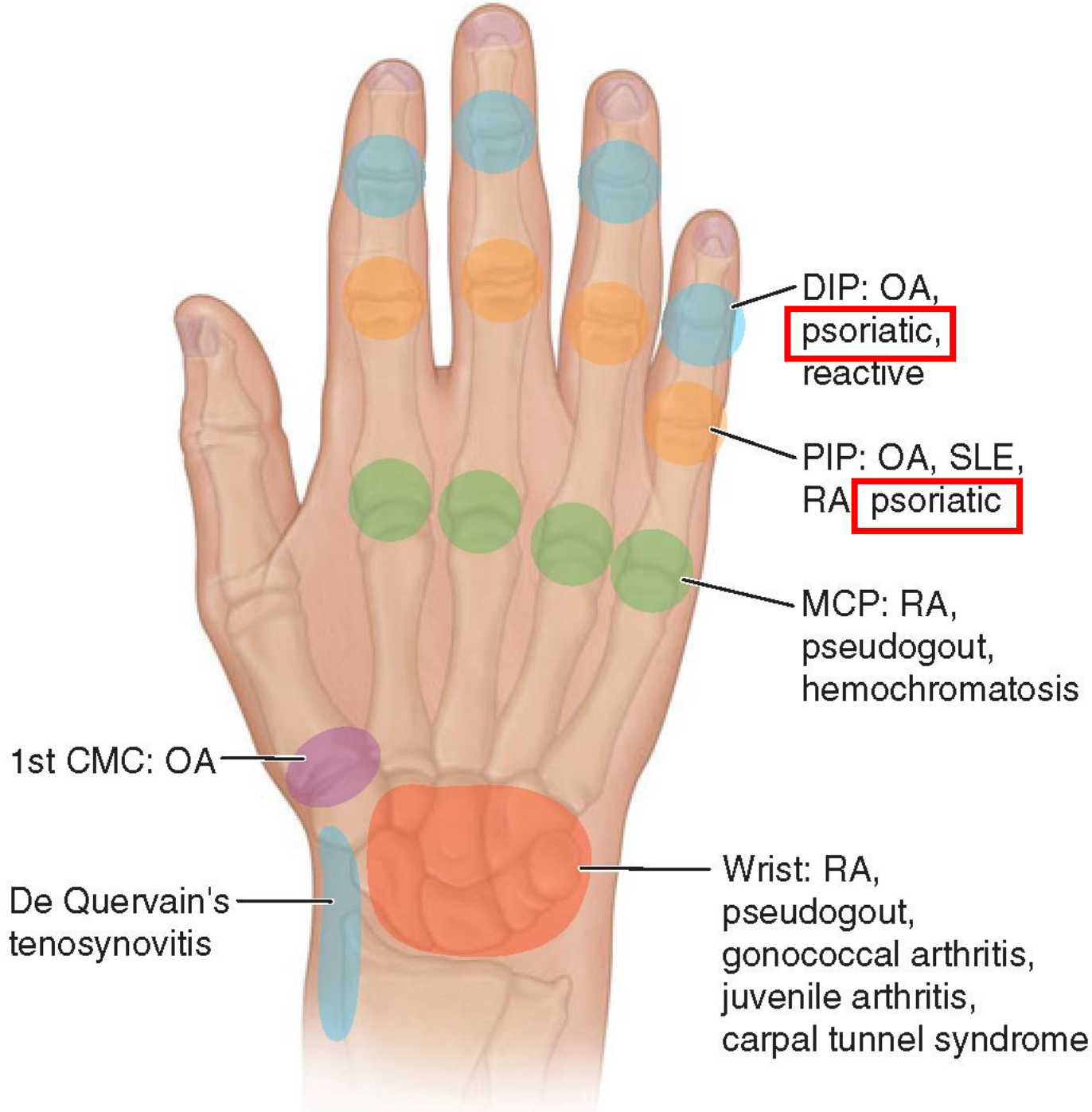
Manifestations of PsA

Two high-yield questions to screen for PsA:

1. Have you had painful or swollen joints?
2. Do you feel stiffness in your joints or back when you wake up? If "yes"
   - How long does it last?
   - Does it improve or worsen with activity?

Stiffness that lasts >30 minutes and improves with activity is suggestive of PsA

- Elmets CA, et al. *J Am Acad Dermatol*. 2019;80(4):1073-1113.


DIP: OA, psoriatic, reactive
PIP: OA, SLE, RA psoriatic
MCP: RA, pseudogout, hemochromatosis
1st CMC: OA
De Quervain's tenosynovitis
Wrist: RA, pseudogout, gonococcal arthritis, juvenile arthritis, carpal tunnel syndrome

Choosing a biologic in adults:

TNF inhibitors great in:

- Psoriatic arthritis (peripheral and axial)
- Pregnancy (certolizumab)

Avoid TNF inhibitors in:

- Demyelinating disease
- Hepatitis B

TNF inhibitors not preferred:

- History of latent tuberculosis
- Advanced CHF

IL-17 inhibitors great in:

- Robust psoriasis efficacy
- Psoriatic arthritis (peripheral and axial)

Avoid IL-17 inhibitors in:

- Personal history of inflammatory bowel disease

Other consideration:

- Oral candidiasis

IL-23 inhibitors great in:

- Robust psoriasis efficacy
- Efficacy in psoriatic arthritis (guselkumab, risankizumab, and ustekinumab)
- Fewer injections

IL-23 inhibitors with evolving evidence:

- psoriatic arthritis involving spine

Laboratory Monitoring before Starting a Biologic per AAD/NPF 2019 Guidelines

- Baseline
  - TB, CBC, CMP, hepatitis B&C. [HIV at provider's discretion].
- Ongoing:
  - TB yearly in high-risk group (contact with people with active TB) and those on TNF inhibitors.

--"Ongoing CBC and CMP are not supported by evidence and are to be assessed at the discretion of each physicians' criteria except in cases involving patients treated with infliximab, for whom it is recommended that liver function tests be repeated every 3 mo after initiation, and if the result is normal, every 6-12 mo thereafter."
--TB test– PPD, T-spot, or quantiferon gold.

Candidates for Dose Escalation:

- **Obese** Patients
- Initial good response waned

General strategy for dose escalation: More frequent injections (shorten the interval between the injections)

Dose escalation for TNF inhibitors for psoriasis

Biologic	FDA-Approved Maintenance Dose	Escalated Dose for Maintenance
Etanercept	50mg once weekly	50mg twice weekly
Adalimumab	40mg every 2 weeks	40mg once weekly
Certolizumab	400mg every 2 weeks. Another option: for patients weighing <198 lbs, 400mg at weeks 0, 2, and 4, then 200mg every 2 weeks.	
Infliximab	5mg/kg every 8 weeks	5mg/kg every 4-8 weeks and/or up to 10mg/kg

Menter et al. J Am Acad Dermatol. 2019 Apr;80(4):1029-1072.

Dose escalation for IL-17 Inhibitors for psoriasis

Biologic	FDA-Approved Maintenance Dose	Escalated Dose for Maintenance
Secukinumab	300mg every 4 weeks	300 mg every 2 weeks*
Ixekizumab	80mg every 4 weeks	80mg every 2 weeks
Brodalumab	210mg every 2 weeks	

*AWA additional recs

Menter et al. J Am Acad Dermatol. 2019 Apr;80(4):1029-1072.

Dose escalation for IL12/23 Inhibitor and IL-23 Inhibitors for psoriasis

Biologic	FDA-Approved Maintenance Dose	Escalated Dose for Maintenance
IL-12/23 Inhibitor		
Ustekinumab	≤100kg: 45mg every 12 weeks >100kg: 90mg every 12 weeks	≤100kg: 90mg every 8-12 weeks >100kg: 90mg every 8-12 weeks
IL-23 Inhibitors		
Guselkumab	100mg every 8 weeks	
Tildrakizumab	100mg every 12 weeks	
Risankizumab	150mg every 12 weeks	

Menter et al. J Am Acad Dermatol. 2019 Apr;80(4):1029-1072.

Switching and Dose Escalation

Primary versus secondary failure to a biologic

- Primary failure: A patient who has never responded optimally to a biologic

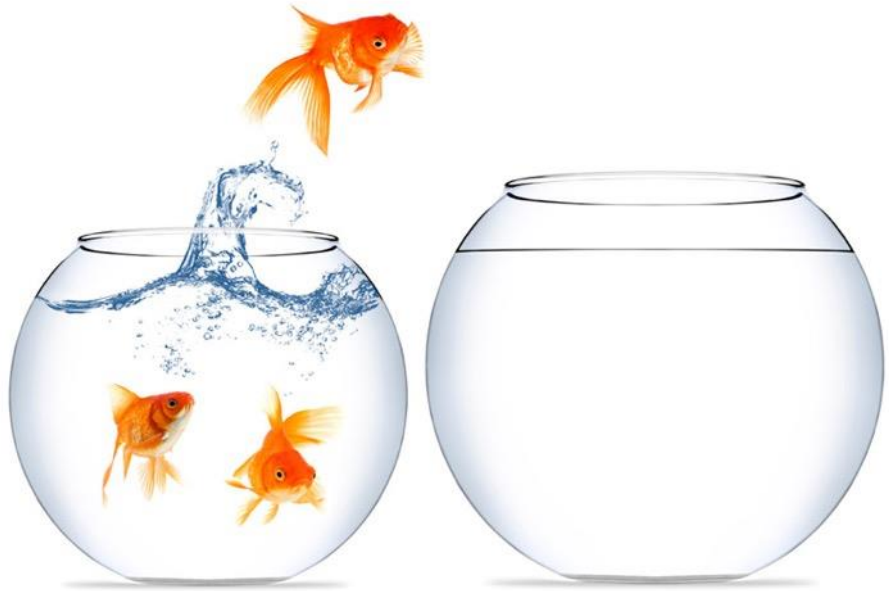
- Secondary failure: A patient who responded initially to a biologic but lost response over time

Primary Failure: Switching Biologics

- Primary failure: A patient who has never responded optimally to a biologic
- Wait at least 6 months to switch, in general
- Consider switching to another class of biologics.

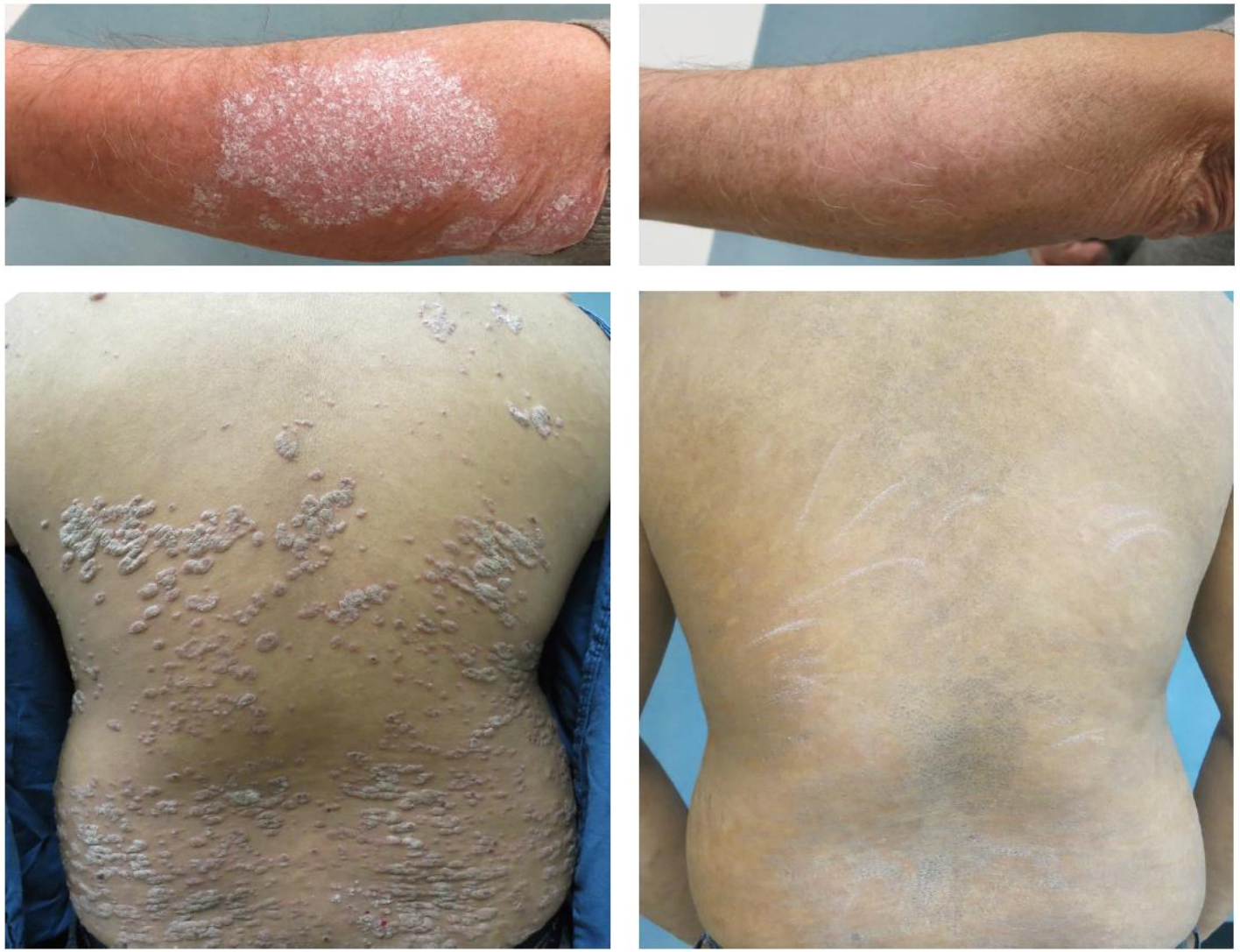
Secondary Failure:
Dose Escalation or Switching Biologics

- If the patient had responded to the biologic for a long time and then lost response (secondary failure), then
  - Dose escalation
  - within class switch: if it helps to address comorbidities such as PsA
  - across-class switching



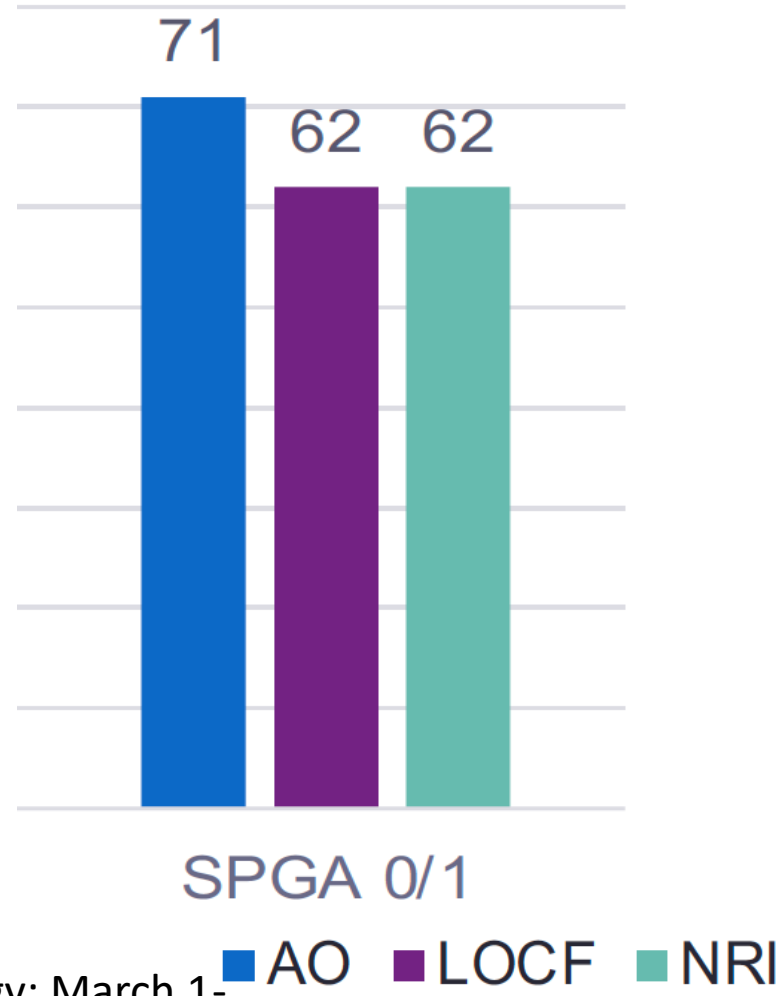
Brodalumab in Patients who failed other IL-17 inhibitors

Figure. Skin clearance of patients who received brodalumab.



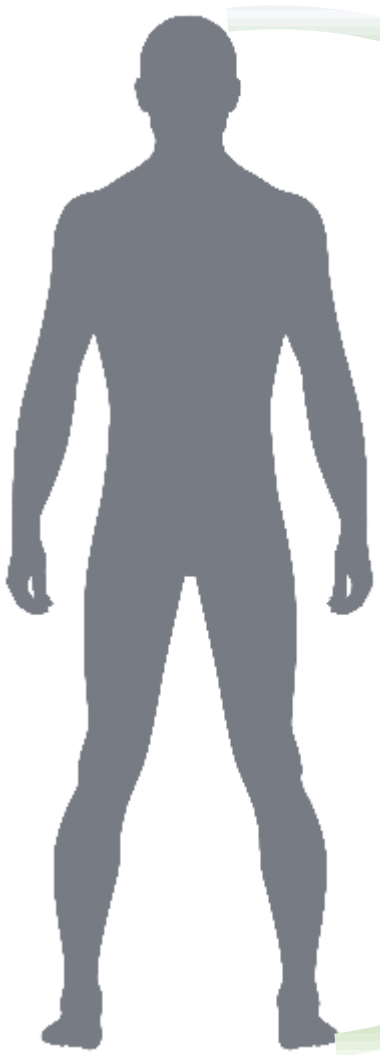
Approximately 40 patients failed treatment with secukinumab or ixekizumab

% patients achieving clear or almost clear



Kimmel et al. Presented at: 77th Meeting of the American Academy of Dermatology; March 1-

Overview of Comorbidities in Psoriasis



Psoriatic arthritis

Cardiometabolic diseases

- Obesity
- Diabetes/Insulin resistance
- Hypertension
- Dyslipidemia
- Myocardial Infarction
- Stroke
- Vascular diseaases
- CV deaths

Inflammatory bowel disease

Mental Health

Other

- Malignancy
- Renal disease
- Sleep apnea
- COPD
- Uveitis
- Hepatic disease

- COPD=Chronic Obstructive Pulmonary Disease.

Elmets CA, et al. *J Am Acad Dermatol*. 2019;80(4):1073-1113.

Psoriasis

?

Cardiovascular diseases

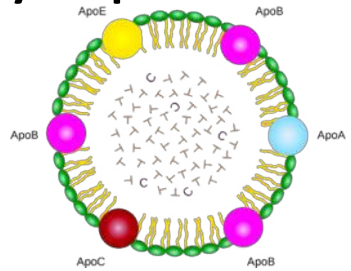
?

Diabetes/insulin resistance

Obesity

Hypertension

Dyslipidemia



AAD/NPF Guidelines 2019: Psoriasis and Cardiovascular Comorbidities

	Recommendation	Strength
2.1	CV risk assessment (screening for HTN, DM, and hyperlipidemia) with national guidelines is recommended for all patients with psoriasis	B
2.2	Consider early and more frequent screening for HTN, DM, and hyperlipidemia in candidates for systemic or phototherapy or those who have psoriasis involving >10% BSA	B
2.3	Risk score models should be adapted by introducing a 1.5 multiplication factor when the patient meets either • Disease severity of BSA >10% • Candidate for systemic or phototherapy	C
2.4	CV risk management should be performed by either a primary care physician or other healthcare provider experienced in CV risk management or the dermatologist	C

AAD = American Academy of Dermatology; NPF = National Psoriasis Foundation; CV = cardiovascular; HTN = hypertension; DM = diabetes mellitus.

Elmets CA, et al. *J Am Acad Dermatol*. 2019;80(4):1073-1113.

Screening Recommendations (US)

Type	Criteria	Frequency
Hypertension	Normal BP <120/80 mmHg	
	Age 18-39 years, no risk factors, and BP <130/85 mmHg	Every 3-5 years
	Age >40 years and those at increased risk for high BP (BP 130-139/85-89 mmHg, overweight/obese, black)	Yearly
Diabetes	Adults aged 40-70 years with BMI ≥25 kg/m^2	Every 3 years
	In those without any risk factors, testing should begin at age 45 years	
Cardiovascular risk assessment	Adults aged 20-79 years with standard risk factors (including hypercholesterolemia, obesity)	Every 4-6 years
	Adults aged 40-79 years: estimate 10-year risk	

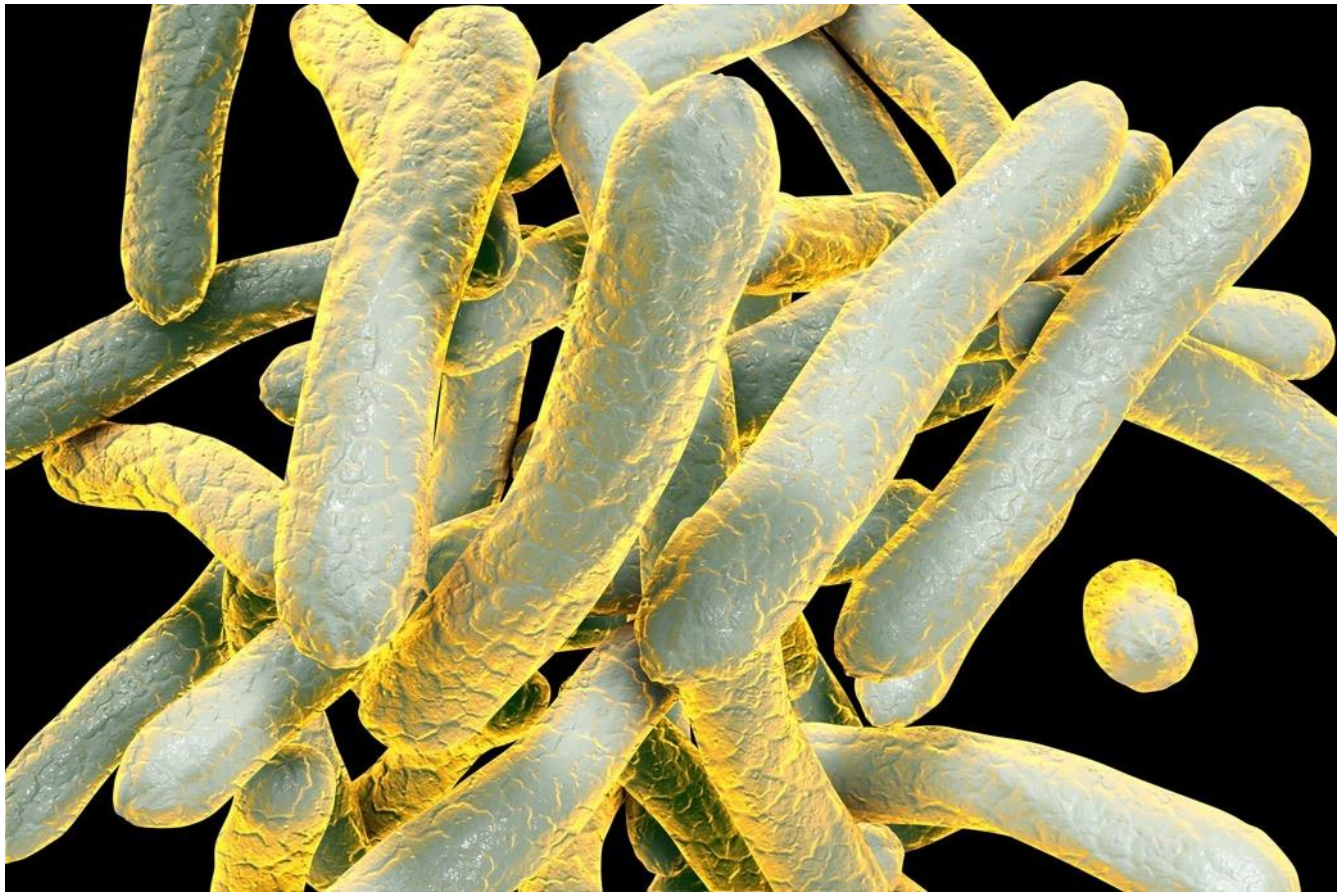
Elmets CA, et al. *J Am Acad Dermatol*. 2019;80(4):1073-1113.

Patients with a History of Malignancy

- History of internal solid-tumor malignancy in remission for ≥ 5 years
  - IL-12/23 with the most safety data, followed by IL-17 and IL-23 inhibitors
  - TNF inhibitors data mixed, but generally considered safe as well.
- History of liquid tumors regardless of remission status (lymphomas and leukemias), and history of internal solid-tumor malignancy in remission for < 5 years, active liquid or solid internal malignancy
  - Avoid biologic medications in general
- History of keratinocyte carcinomas (cutaneous SCC, BCC)
  - Use of biologics permissible with regular skin checks

Tuberculosis

- **Risk factors** for reactivation of latent TB: HIV/AIDS, transplantation, TNF-α blockers, close contacts, kidney dialysis
- Risk of reactivation of latent TB is much lower with IL-17 inhibitors and IL-23 inhibitors compared to TNF inhibitors



HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome.

Latent TB Treatment: 6- to 9-Month Regimen with Isoniazid Monotherapy

Drug(s)	Duration	Dose	Frequency	Total Doses
Isoniazid (INH)	6 months	Adults: 5 mg/kg Children: 10–20 mg/kg Maximum dose: 300 mg	Daily	180
		Adults:15 mg/kg Children: 20–40 mg/kg Maximum dose: 900 mg	Twice weekly	52
	9 months	Adults: 5 mg/kg Children: 10–20 mg/kg Maximum dose: 300 mg	Daily	270
		Adults: 15 mg/kg Children: 20–40 mg/kg Maximum dose: 900 mg	Twice weekly	76

CDC. Accessed August 9, 2021. https://www.cdc.gov/tb/topic/treatment/ltbi.htm.

Drug(s)	Duration	Dose	Frequency	Total Doses
Isoniazid (INH) and Rifapentine (RPT)	3 months	Adults and Children aged 12 years and older: INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg 900 mg maximum Children aged 2–11 years: INH 25 mg/kg; 900 mg maximum RPT as above	Once weekly	12
Rifampin (RIF)	4 months	Adults: 10 mg/kg Children: 15–20 mg/kg Maximum dose: 600 mg	Daily	120
Isoniazid (INH) and Rifampin)	3 months	Adults: INH 5 mg/kg; 300 mg maximum RIF 10 mg/kg; 600 mg maximum Children: INH 10-20 mg/kg; 300 mg maximum RIF 15-20 mg/kg; 600 mg maximum	Daily	90

Latent TB Treatment: 3- to 4-Month Regimen

CDC. Accessed August 9, 2021. https://www.cdc.gov/tb/topic/treatment/ltbi.htm.

Thank you!

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