STARTING AN IL-17 INHIBITOR AND TOUGH CASES

Kristine Kucera, PA-C, MPAS, DHS
US Dermatology Partners
Richardson, TX

Clinical Professor
UT Southwestern Medical Center
Dallas, TX

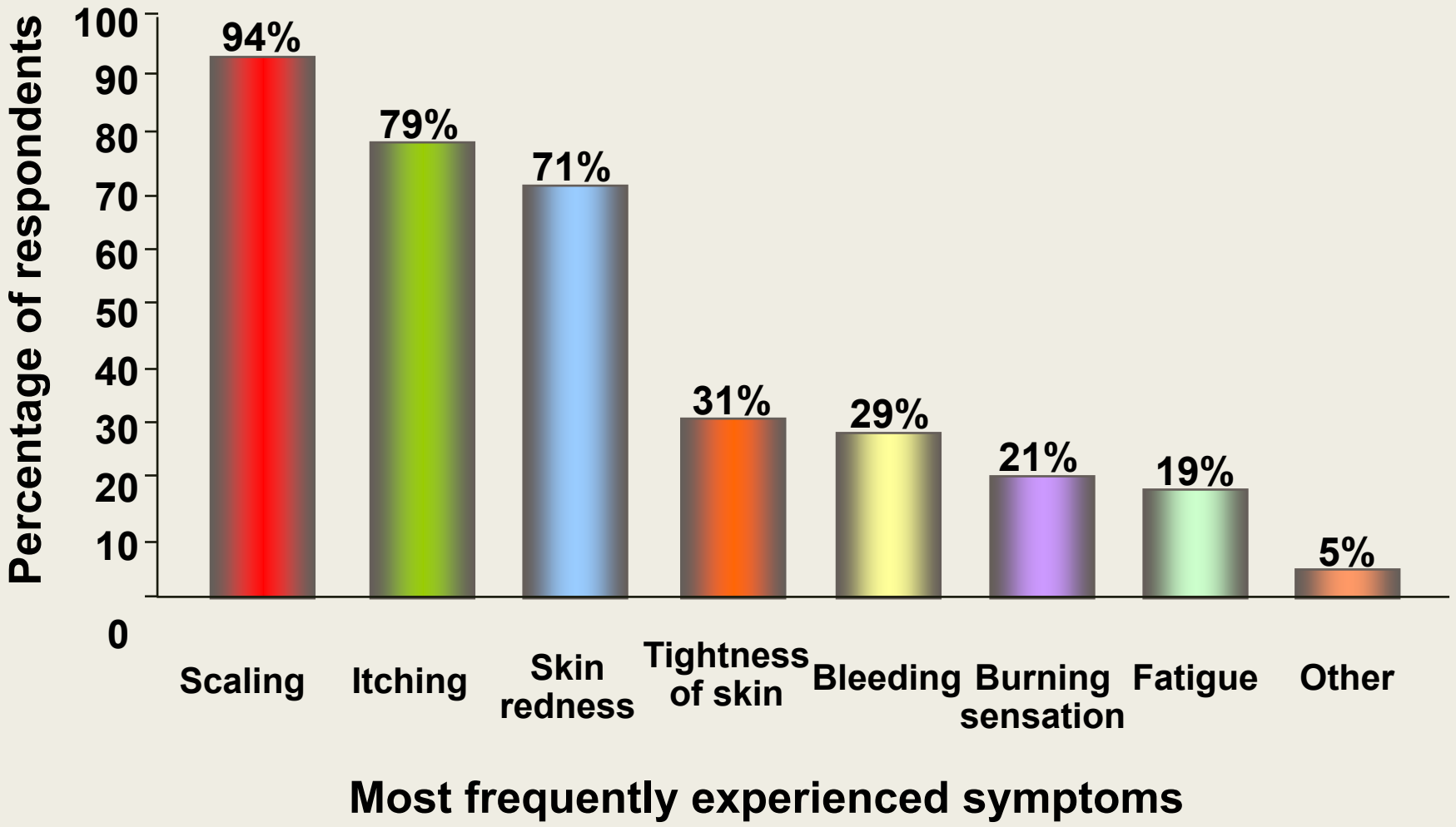
Learning Objectives

- Know the different IL-17 inhibitors used in Psoriatic disease
- Understand the basic science of inflammatory disease and how IL-17 inhibitors work
- Identify if an IL-17 inhibitor is the right treatment choice for the patient, potential adverse events, and monitoring
- Review of tough cases

Psoriasis

- Psoriasis affects 3.2% of American adults (~7.4 million persons); as many as 40% eventually have Psoriatic Arthritis
- Symptoms usually manifest before age 35 but can occur at any time
  - *Onset less than 15 years of age may indicate more severe, resistant disease*
  - *Up to 33% of patients report a family history*
- ~20% of patients have moderate to severe disease; extensive involvement on hands, feet, scalp, or genitals
- Psoriatic diseases negatively affect QoL, productivity, daily function—rated as debilitating as cancer or heart disease

Psoriasis Symptoms



Krueger G, et al. *Arch Dermatol*. 2001;137:280-284.

Pathogenesis

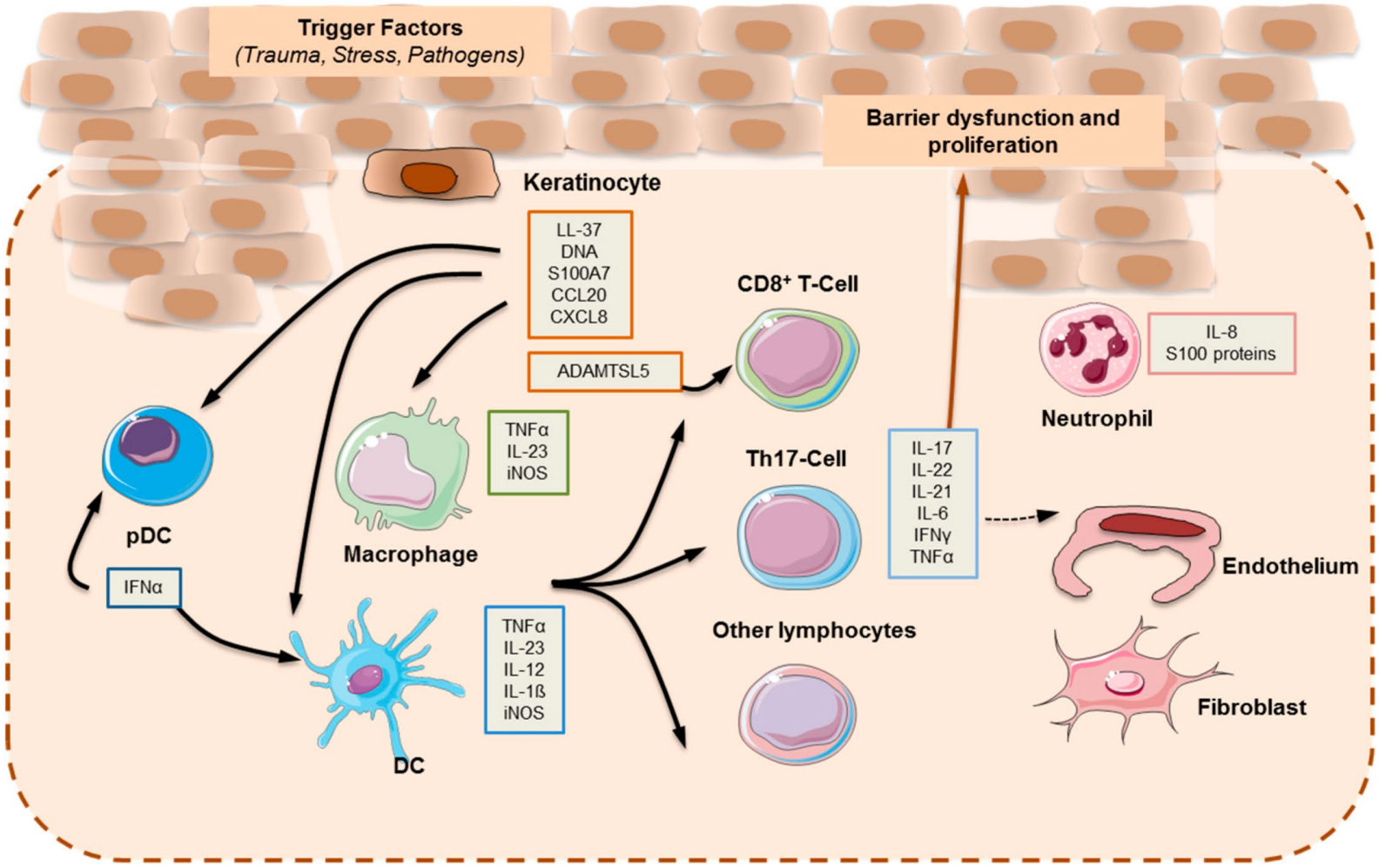
- The hallmark of psoriasis is sustained inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation.
- An initiation phase possibly triggered by trauma (Koebner phenomenon), infection, or drugs.
- A maintenance phase characterized by a chronic clinical progression.
- Dendritic cells (antigen presenting cells) play a major role in the initial stage of disease.
- Activation of these dendritic cells, promotes the secretion of tumor necrosis factor-a, IL-23 and IL-12, which modulates the differentiation and proliferation of Th17 and Th1 cell subsets.
- The activation of the adaptive immune response via the distinct T cell subsets drives the maintenance phase of psoriatic inflammation.
- Th17 cytokines, namely IL-17, IL-21, and IL-22 activate keratinocyte proliferation in the epidermis.

Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. *International Journal of Molecular Sciences*. 2019; 20(6):1475

Pathogenesis

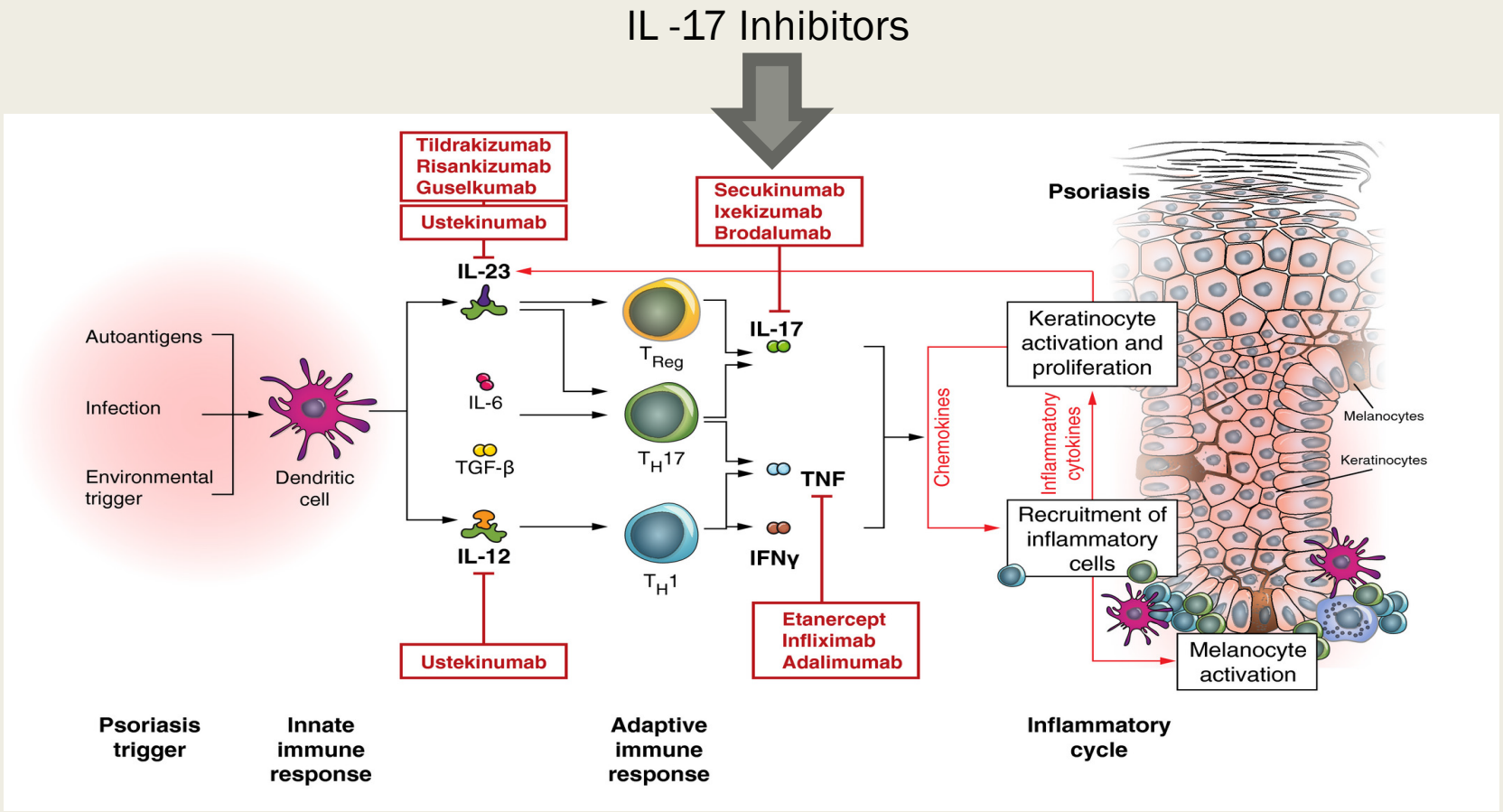
- The TNFα–IL-23–Th17 inflammatory pathway characterizes plaque-type psoriasis.
- The IL-17 cytokine family is composed of six members: IL-17A–F.
- They are produced by different cell types and are important regulators of inflammatory responses.
- The clinically relevant signaling in psoriasis is mediated mostly by IL-17A and IL-17F; both act through the same receptor but have different potencies. IL-17A exerts a stronger effect than IL-17F.
- Three human monoclonal antibodies targeting IL-17 are available. Secukinumab and ixekizumab block IL-17A; whereas brodalumab is directed against the IL-17 receptor A.
- IL-17-targeted biologics are fast acting, showing significant differences from placebo within the first week of treatment.

Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. *International Journal of Molecular Sciences*. 2019; 20(6):1475



Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. *International Journal of Molecular Sciences*. 2019; 20(6):1475

Immune Axis in Psoriasis (Pathogenesis/Treatment)



Journal of the European Academy of Dermatology and Venereology, Volume: 31, Issue: 10, Pages: 1616-1626, First published: 27 June 2017, DOI: (10.1111/jdv.14433)

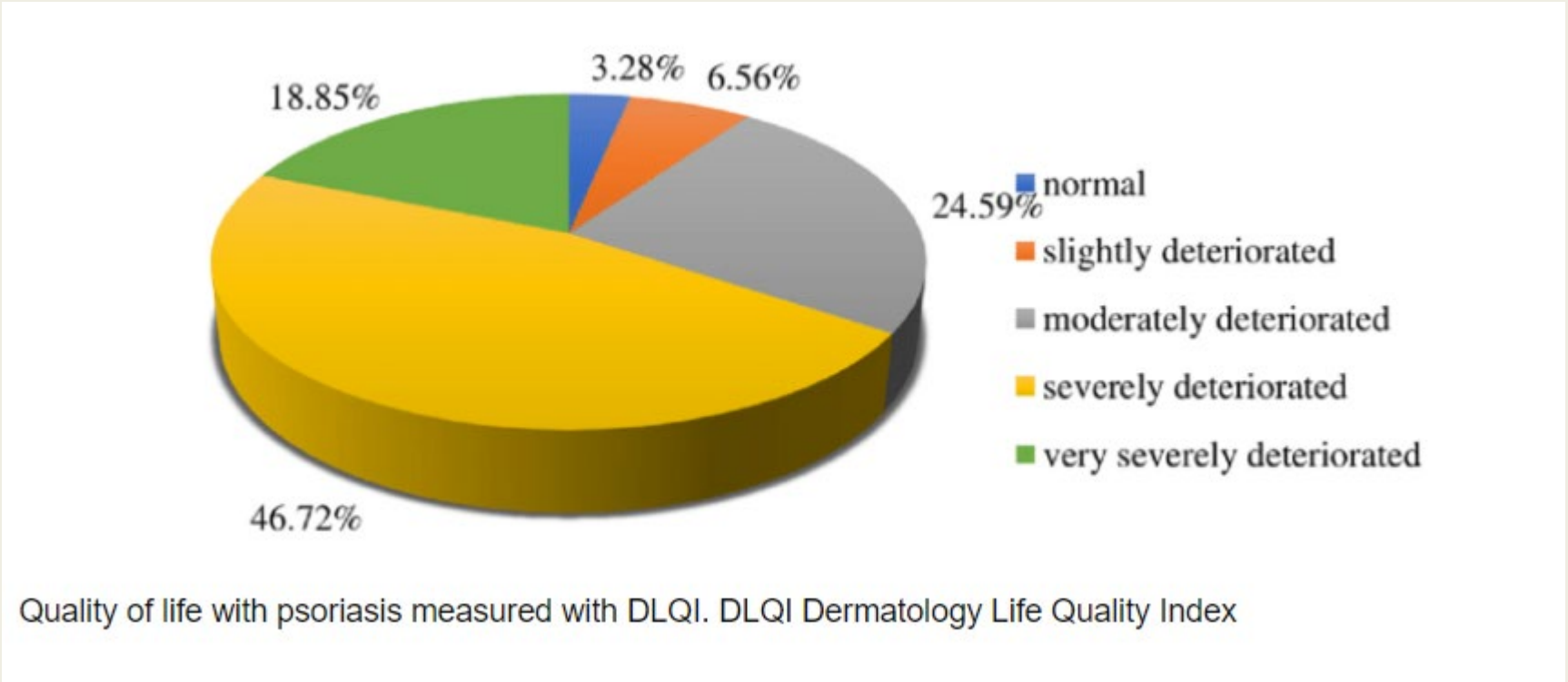
Biologic Therapies: IL -17 Inhibitors for Moderate to Severe Psoriatic Disease

Indication(s)		Recommended Dosage (Adults)	Boxed Warning
IL-17A Inhibitors and Targets of IL-17 Receptor			
Brodalumab (Siliq)	PsO	210 mg SQ wk 0, 1, 2, then 210 mg q2wk	Suicidal ideation and behavior
Ixekizumab (Taltz)	PsO, PsA	PsO: 160 mg SQ wk 0; 80 mg wk 2, 4, 6, 8, 10, 12; then 80 mg q4wk PsA: 160 mg SQ wk 0, then 80 mg q4wk	No
Secukinumab (Cosentyx)	PsO, PsA	PsO, PsA with coexisting moderate to severe plaque PsO: 300 mg SQ, wk 0, 1, 2, 3, 4, then q4wk	No

In whom should we consider biologics?

- Moderate to Severe Psoriasis:
  - *Away from "step therapy" to consideration of systemic/biologics therapies first line*
  - *AAD guidelines: >5% BSA or involving functionally important areas regardless of BSA (genital, hands and feet)*
  - *Insurers/Payers: BSA ≥ 10%, PGA ≥ 3, PASI ≥12*
- Active psoriatic arthritis
- Others: Treatment goals not met; reduced **Quality of Life**.
  - *Decreased QOL can push mild psoriasis to moderate or severe*

Quality of Life



Quality of life with psoriasis measured with DLQI. DLQI Dermatology Life Quality Index

Acceptance of Illness, Satisfaction with Life, Sense of Stigmatization, and Quality of Life among People with Psoriasis: A Cross-Sectional Study Article in Dermatology and Therapy · March 2020 DOI: 10.1007/s13555-020-00368-w

What is DLQI

The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one or two minutes.

SCORING

The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question 7, 'prevented work or studying'	scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

HOW TO INTERPRET MEANING OF DLQI SCORES

0 – 1	no effect at all on patient's life
2 – 5	small effect on patient's life
6 – 10	moderate effect on patient's life
11 – 20	very large effect on patient's life
21 – 30	extremely large effect on patient's life

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1. Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?
   - Very much ❒
   - A lot ❒
   - A little ❒
   - Not at all ❒

2. Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?
   - Very much ❒
   - A lot ❒
   - A little ❒
   - Not at all ❒

3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?
   - Very much ❒
   - A lot ❒
   - A little ❒
   - Not at all ❒
   - Not relevant ❒

4. Over the last week, how much has your skin influenced the **clothes** you wear?
   - Very much ❒
   - A lot ❒
   - A little ❒
   - Not at all ❒
   - Not relevant ❒

5. Over the last week, how much has your skin affected any **social** or **leisure** activities?
   - Very much ❒
   - A lot ❒
   - A little ❒
   - Not at all ❒
   - Not relevant ❒

6. Over the last week, how much has your skin made it difficult for you to do any **sport**?
   - Very much ❒
   - A lot ❒
   - A little ❒
   - Not at all ❒
   - Not relevant ❒

7. Over the last week, has your skin prevented you from **working** or **studying**?
   - Yes ❒
   - No ❒
   - Not relevant ❒

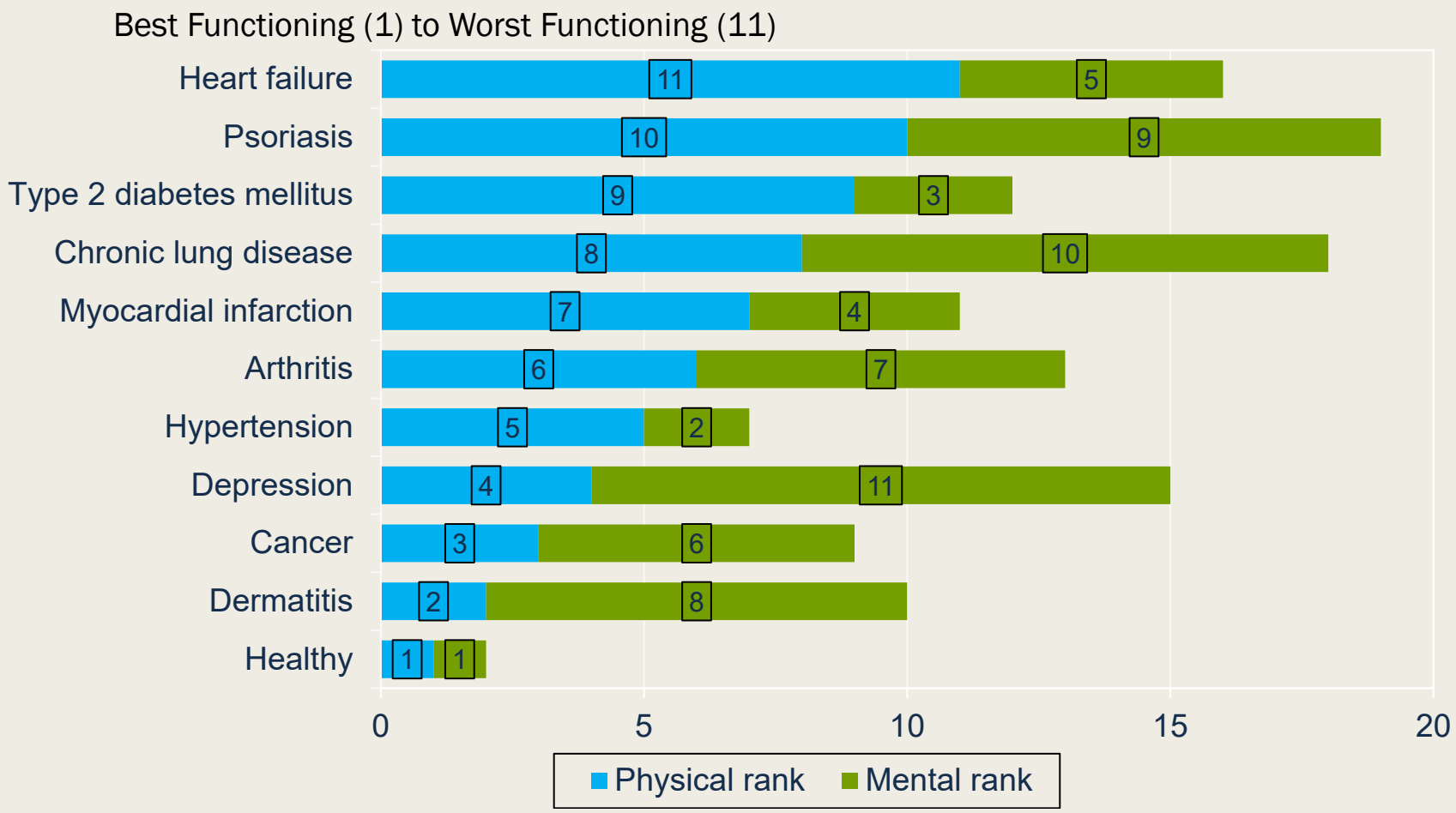
   If "No", over the last week how much has your skin been a problem at **work** or **studying**?
   - A lot ❒
   - A little ❒
   - Not at all ❒

8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?
   - Very much ❒
   - A lot ❒
   - A little ❒
   - Not at all ❒
   - Not relevant ❒

9. Over the last week, how much has your skin caused any **sexual difficulties**?
   - Very much ❒
   - A lot ❒
   - A little ❒
   - Not at all ❒
   - Not relevant ❒

10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?
    - Very much ❒
    - A lot ❒
    - A little ❒
    - Not at all ❒
    - Not relevant ❒

Physical and Mental Rankings of Psoriasis and Other Diseases



Van Voorhees AS, et al. www.psoriasis.org/sites/default/files/npf_pocketguide_2018_0010.pdf. Accessed May 23, 2019.

NPF Treatment Target for Psoriasis Is ≤1% of BSA

Preferred assessment instrument in clinical practice	BSA
Acceptable response after treatment initiation	Either BSA ≤3% or BSA improvement ≥75% from baseline at 3 months after treatment initiation
Target response after treatment initiation	BSA ≤1% at 3 months after treatment initiation
Target response during maintenance therapy	BSA ≤1% at every 6-month assessment interval during maintenance therapy

Set a target goal of complete/near-complete skin clearance in patients with moderate to severe psoriasis

Armstrong AW, et al. *J Am Acad Dermatol.* 2017;76:290-298.

Considerations applicable to all biologics for psoriasis prior to initiation and during maintenance

- Assess for TB
- Assess underlying cancer risk
- Verify absence of active infection
- Consider completing all age-appropriate immunizations

TB=tuberculosis. CHF=congestive heart failure. CD=Crohn's disease. UC=ulcerative colitis.

Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics
JAAD Volume 80, Issue 4, P1029-1072. April 01, 2019

Biologic-class specific considerations (per prescribing information)

IL-17 inhibitors

- Exercise caution in patients with CD/UC when considering IL-17 inhibitors
- Evaluate for depression and suicidality with brodalumab

CD=Crohn's disease. UC=ulcerative colitis.

Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics
JAAD Volume 80, Issue 4, P1029-1072. April 01, 2019

IL -17 Efficacy/Safety

- Singh, R., Balogh, E.A. & Feldman, S.R. Update on IL-17 Inhibitors for Psoriasis. *Curr Derm Rep* 9, 339–352 (2020)
  - *In multiple phase III clinical trials, IL-17 inhibitors were more efficacious than placebo or slightly more efficacious in comparisons to many other systemic and biologic treatments.*
  - *Overall, IL-17 inhibitors have a fairly mild side effect profile for use in psoriasis.*

- IL17-Inhibition
  - *Serious infections*
  - *Candidiasis*
  - *Neutropenia*
  - *Crohn's disease worsening*

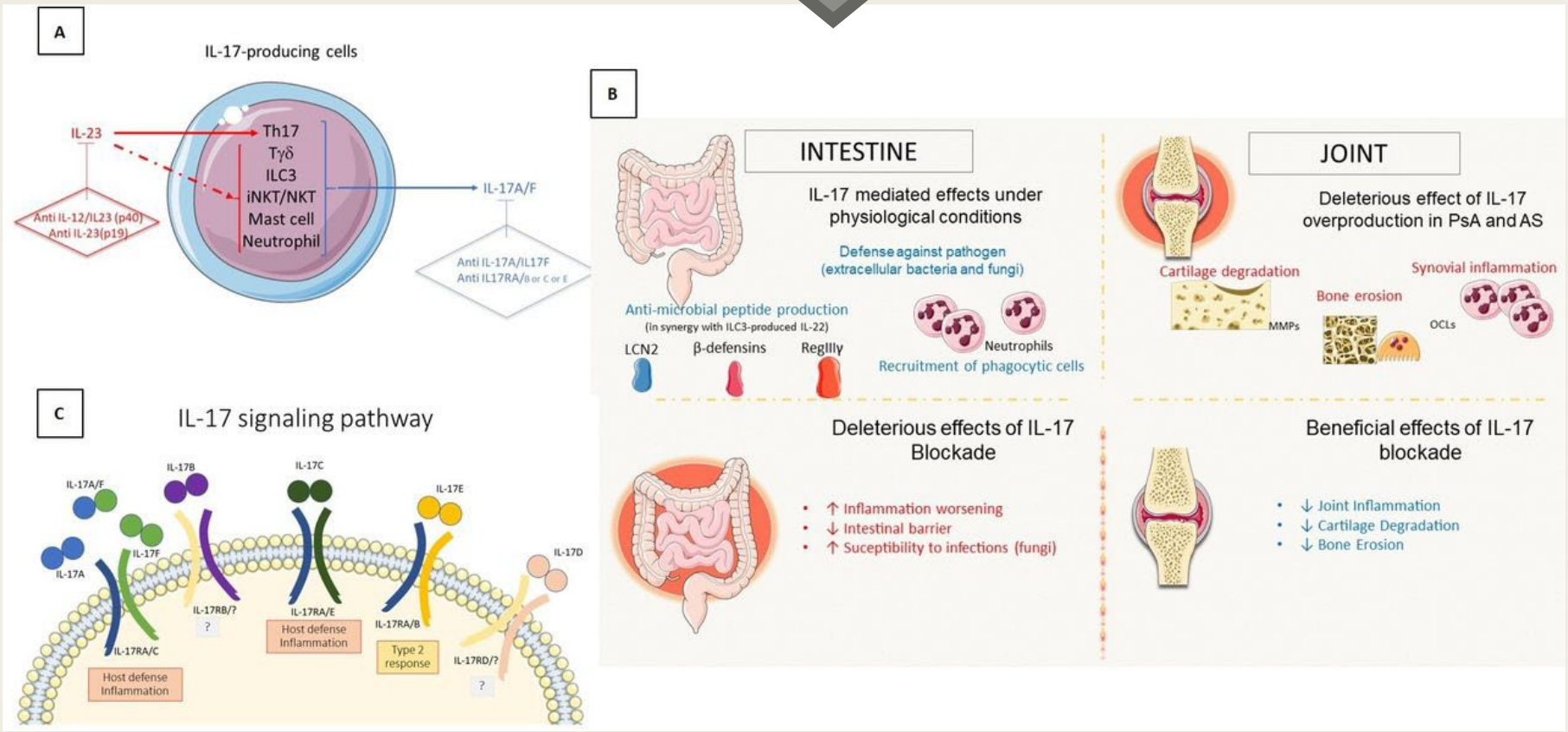
- IL-17A inhibitors
  - *No new safety signals with increasing duration of exposure*

Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics
JAAD Volume 80, Issue 4, P1029-1072. April 01, 2019

IL -17 Safety

- Fauny M, Moulin D, D'Amico F*, et al*. Paradoxical gastrointestinal effects of interleukin-17 blockers. *Annals of the Rheumatic Diseases* 2020;79:1132-1138
- IL17-Inhibition Specific potential adverse events
  - *Crohn's disease worsening*
  - *Candidiasis*
- What is IL-17 and what does it do?
  - In 2005, a third subset of Th lymphocytes (Th17) was identified that promotes the expression of IL-17A, IL-17F, IL-21 and IL-22.
  - Th17 lymphocytes and IL-17 are involved in the immune response against extracellular pathogens through the regulation of intestinal epithelial permeability and act more specifically in the mucosal interface.
  - Most Th17 cells are found in the lamina propria of the gastrointestinal wall and protect against bacterial and fungal infections.

Inhibition of IL-17 causes a reduction in joint and skin inflammation, but at the same time negatively affects the activity of the intestinal barrier by worsening gut inflammation



Marine Fauny et al. Ann Rheum Dis 2020;79:1132-1138

Monitoring

- Screening for tuberculosis is required before starting a biologic and on a yearly basis
- A CBC and CMP at baseline and yearly
- Hepatitis B and Hepatitis C at baseline and yearly
- Optional HIV screen
- While on therapy, use caution when the patient
  - *Develops an infection*
  - *Plans to have major surgery*
  - *Plans to get a live vaccine (shingles, yellow fever, etc)*
- Every visit: Check progress of skin, New onset of joint or GI symptoms

Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics
JAAD Volume 80, Issue 4, P1029-1072. April 01, 2019

Live Vaccines to Be Avoided When Using Biologics

- Adenovirus
- Cholera
- Herpes zoster (shingles) – Zostavax only*
- Live attenuated viral/intranasal spray for influenza
- Measles, mumps, rubella or measles, mumps, rubella, varicella
- Rotavirus
- Typhoid (live attenuated bacterial oral)
- Varicella
- Vaccinia (smallpox)
- Yellow fever

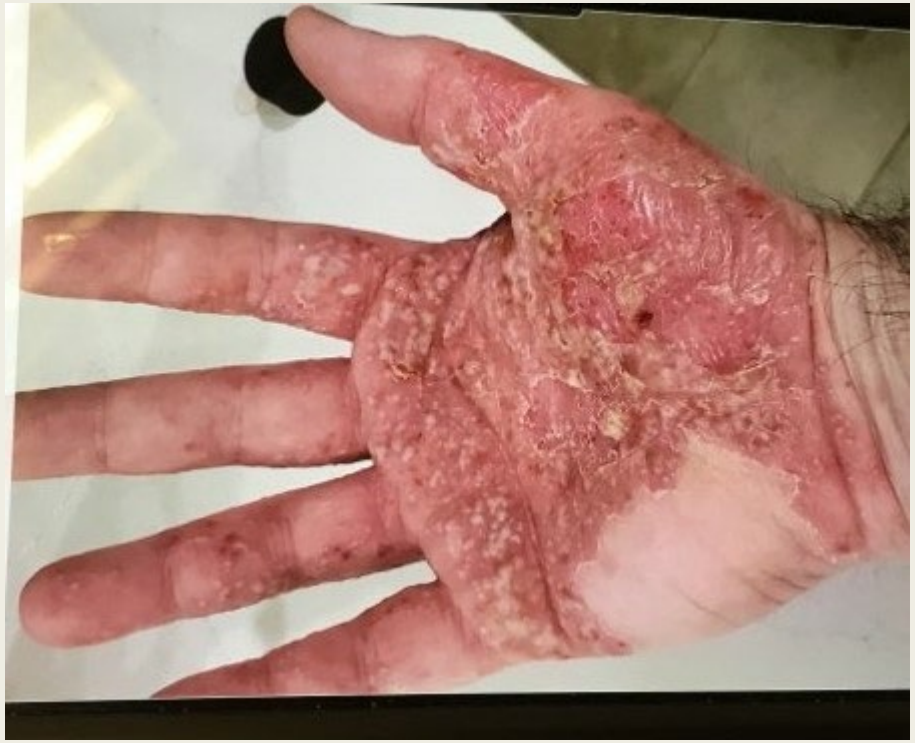
*Shingrix is an inactivated recombinant, adjuvanted (non-live) vaccine for herpes zoster.
Centers for Disease Control and Prevention. www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/us-vaccines.pdf.

Case Study #1

- 47yo male with a 20-year history of plaque psoriasis. Well controlled on Humira 40mg every other week. Initial BSA 18% but has been clear since initiating/responding 6 years ago. No history of PsA
  - *Last injection 1 week prior*
  - *Healthy, PMH – HTN –controlled on Losartan x 3 yrs*
  - *Married, works at bank, nonsmoker, Ht 5'10", Wt 185*
- Presented with new onset Palmar-Plantar pustulosis and "flaring" of his plaque psoriasis x 5 days.
- ??? Cause of change in morphology and flare ???
  - *Strept infection, new medications, stress, surgery, Prednisone*
    - Patient declined all – nothing has changed and no fever, sore throat, etc in the last few weeks.

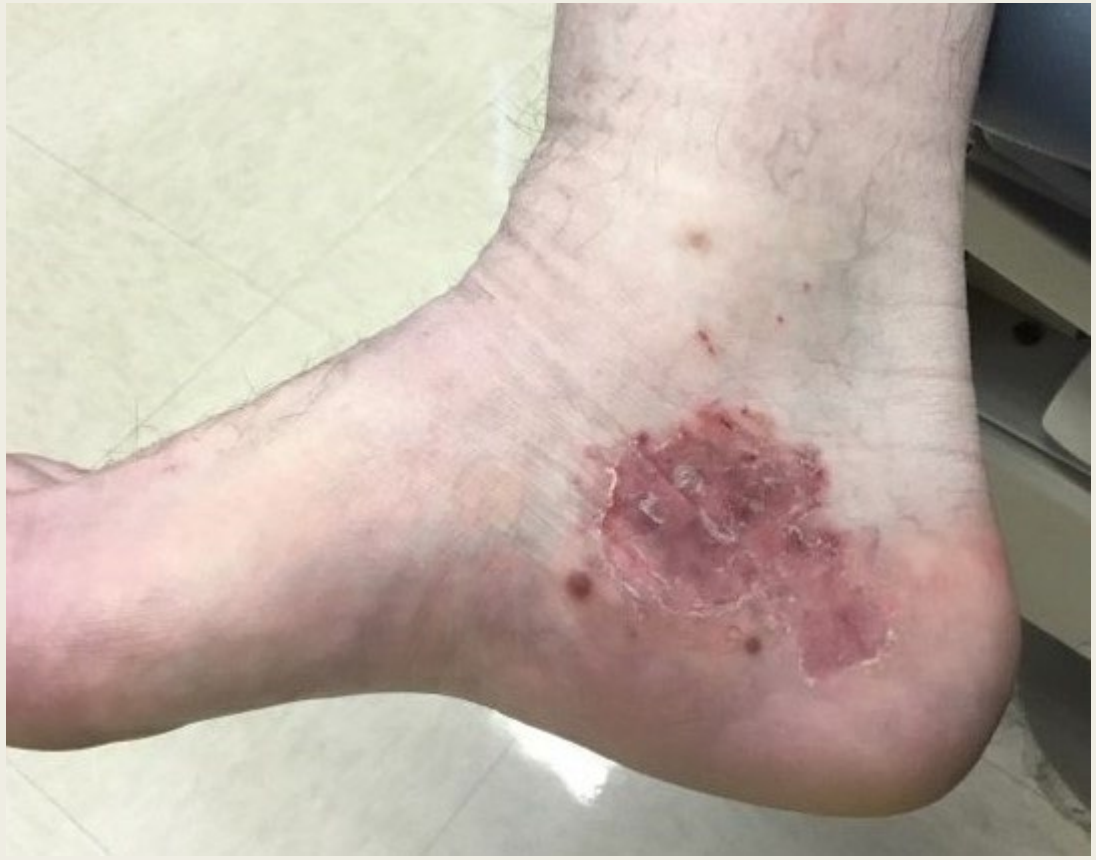
Case Study #1

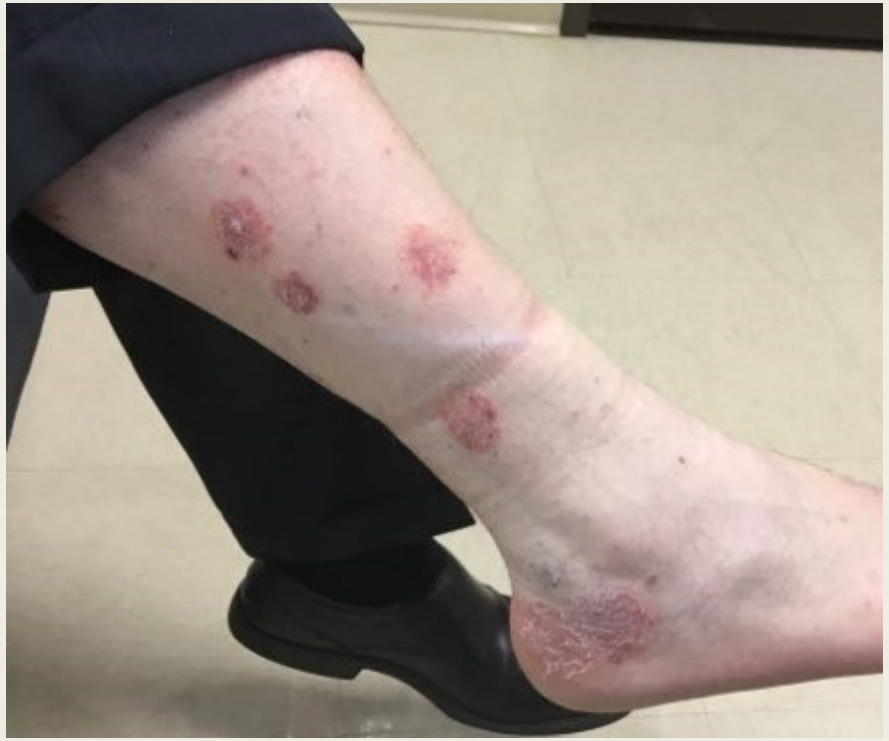
- EXAM: Erythema and scaling with crops of pustules of palms and soles.
- Very inflammatory psoriatic plaques of trunk and legs. BSA-15%



Photos from K. Kucera PAC
With permission from patient.

Case Study #1





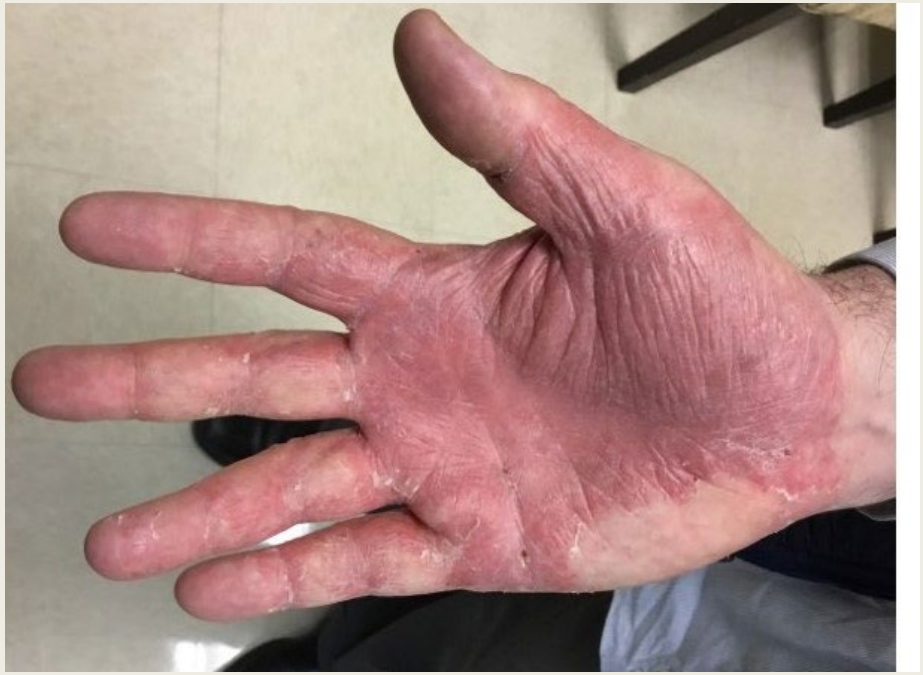
Photos from K. Kucera PAC
With permission from patient.

Case Study #1

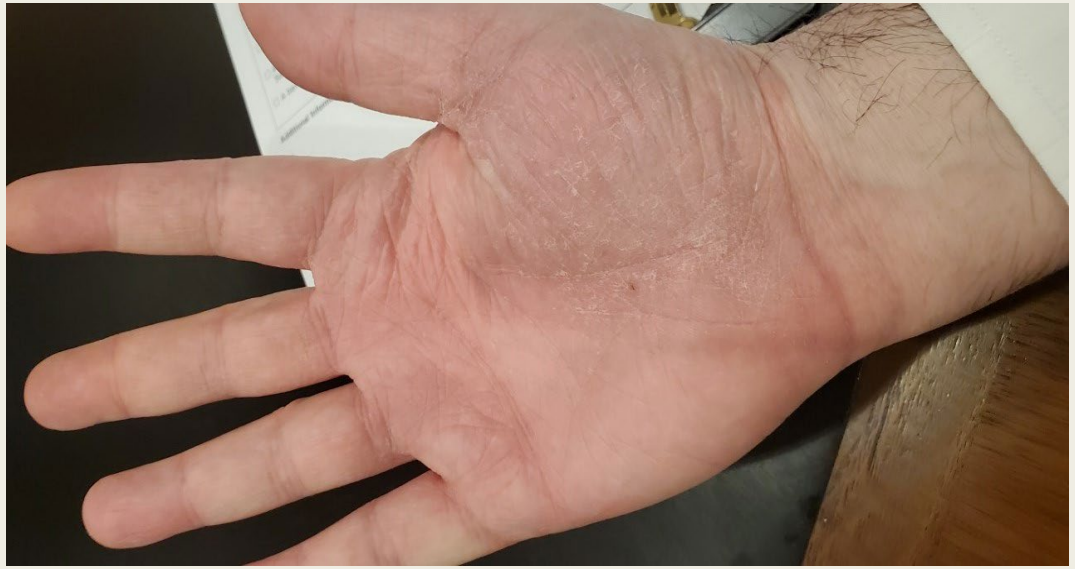
- Decision Points
  - *Patient up to date with yearly labs*
  - *Ordered CBC, CMP to see if anything underlying*
  - *Initiated Augmentin 875mg BID x 10 days*
    - Underlying Strept/Infection
  - *Initiated IL-17 Inhibitor*
    - Rapid onset of action
    - Has shown success in clinical trials in difficult to treat areas (palmar-plantar)
    - Patient does not have a history of Crohns/UC
    - Has shown success in patients with prior biologic experience

48 hours- Labs Results WNL – Finish course of antibiotics (possible strept carrier?)

Case Study #1



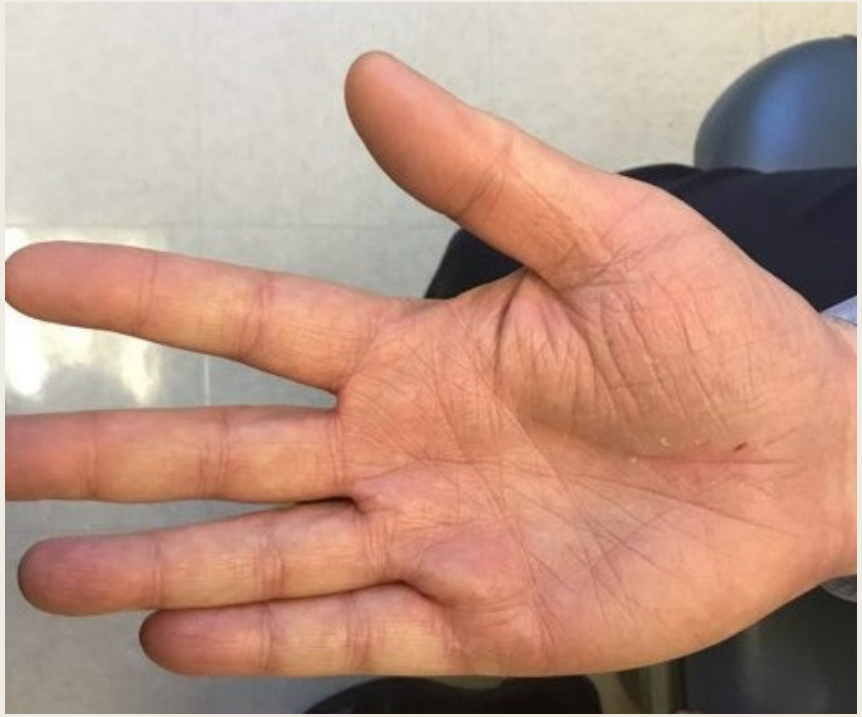
2 Weeks



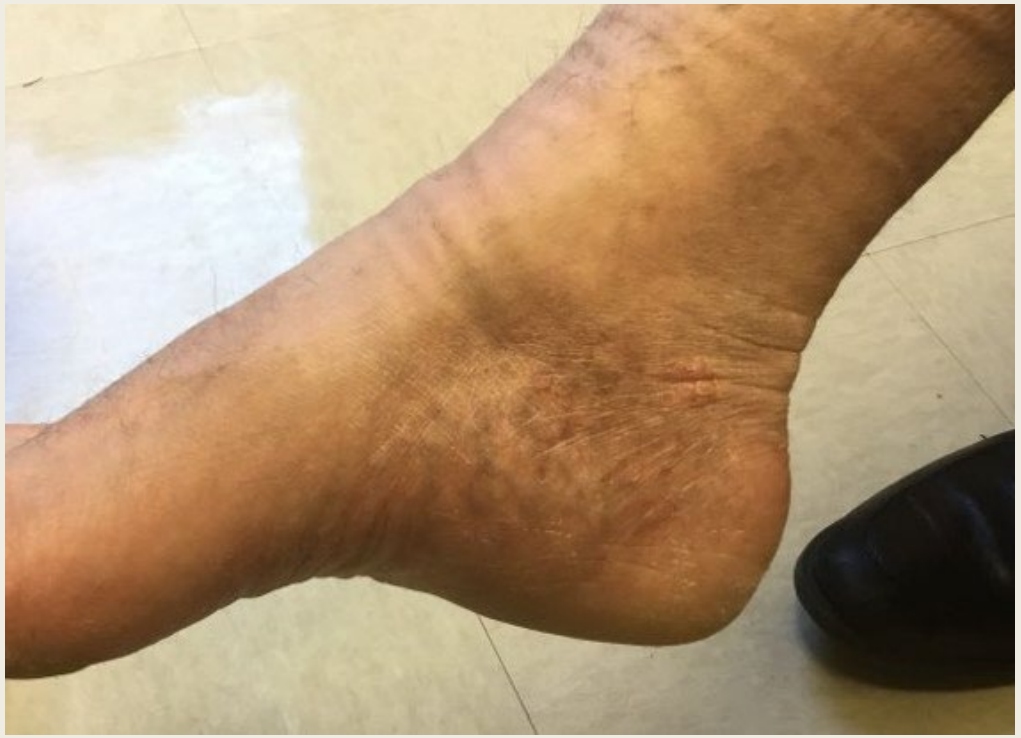
4 Weeks

Photos from K. Kucera PAC
With permission from patient.

Case Study #1



6 Weeks



6 Weeks

Photos from K. Kucera PAC
With permission from patient.

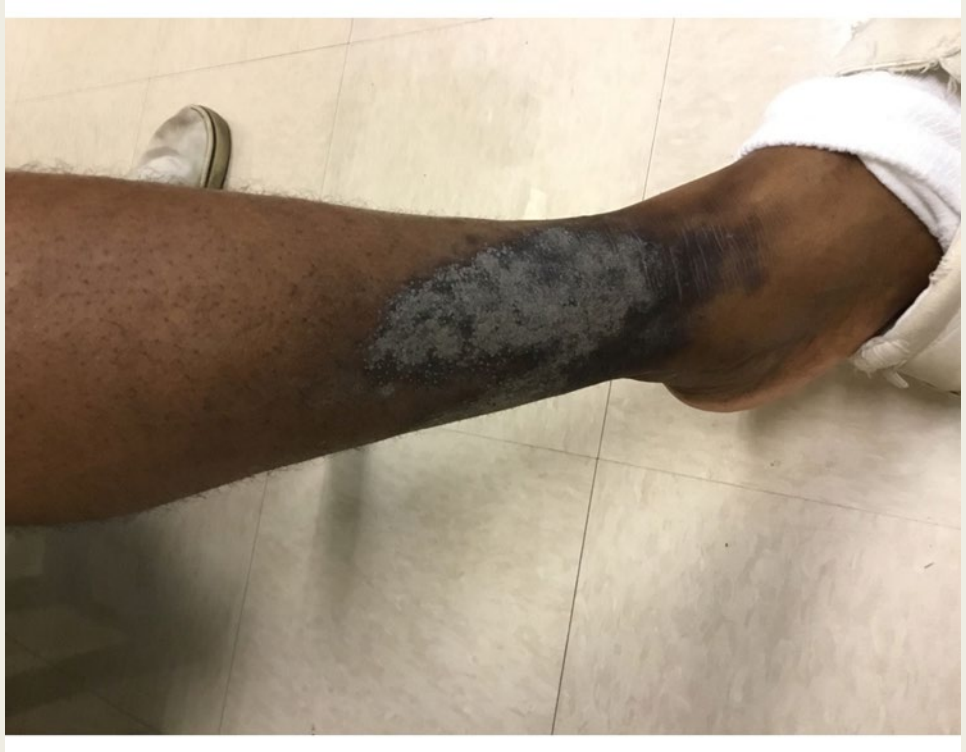
Case Study #2

- 58 yo male with a 10-year history of plaque psoriasis.
  - *Only been treated with topical corticosteroids BSA- 3%-5%*
  - *PMH – HTN –Losartan*
    - *Type 2 Diabetes – Sitagliptin, Metformin*
    - *High Chlosterol – Atorvastatin*
  - *Married, Bus Driver, Ht 5’9”, Wt 260*

- Psoriasis staring to spread and very “itchy”
  - *Finds himself scratching and rubbing his lower legs constantly*
  - *Tired of applying cream and is not helping*

Case Study #2

- EXAM: Scattered 10-25mm erythematous plaques with silvery scale of arms and back.
- Large lichenified confluent plaques of bilateral lower legs. BSA-8%



Photos from K. Kucera PAC
With permission from patient.

Case Study #2

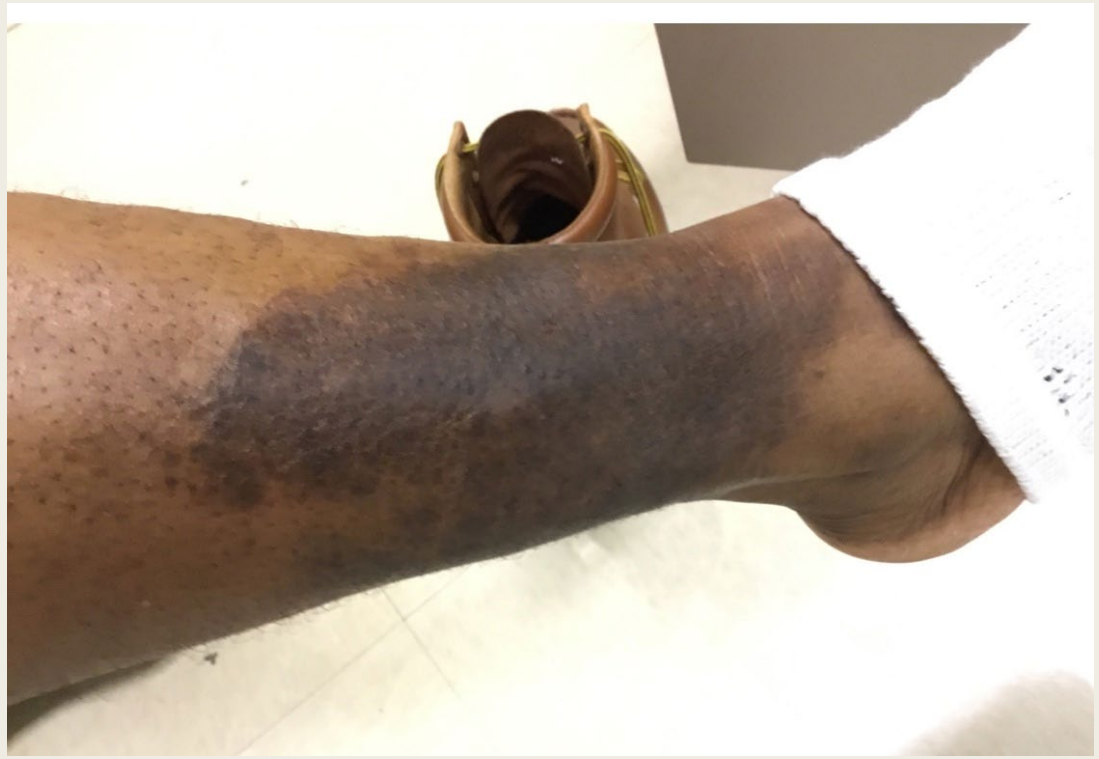
- Decision Points
  - *Patient has small plaque psoriasis on arms and trunk with thick large plaques of lower legs*
  - *Patient admits scratching lower legs which contributes to the thickening of the plaques (Koebner phenomenon)*
  - *Patient has multiple Co-morbidities*
  - *Patient not reporting any PsA signs/symptoms*
  - *Patient has BMI 38.4 – Obese*
  - *Recent studies show that IL-17A plays a role in both psoriasis and obesity and may be a crucial element in the association between the two and the continuous cycle of inflammation**
  - *Initiated IL-17 Inhibitor*
    - Rapid onset of action
    - Has shown success in clinical trials in patients with low and high BMI
    - Patient does not have a history of Crohns/UC
    - Drugs that inhibit the activity of IL-17A have demonstrated efficacy in rapidly reducing itch**

*The Assocation of Psoriasis and Obesity: Focusing on IL-17A-Related Immunological Mechanisms
International Journal of Derm and Venereology June 2021. Volume 4. Issue 2. p116-121.

**Impact of Treatment on Itch in Plaque Psoriasis
Dermatol Ther (Heidelb). 2018 Dec; 8(4): 621–637.

Case Study #2

6 weeks



6 weeks

Photos from K. Kucera PAC
With permission from patient.

Comprehensive, Collaborative, Patient-Centered Care for Patients With Psoriatic Disease