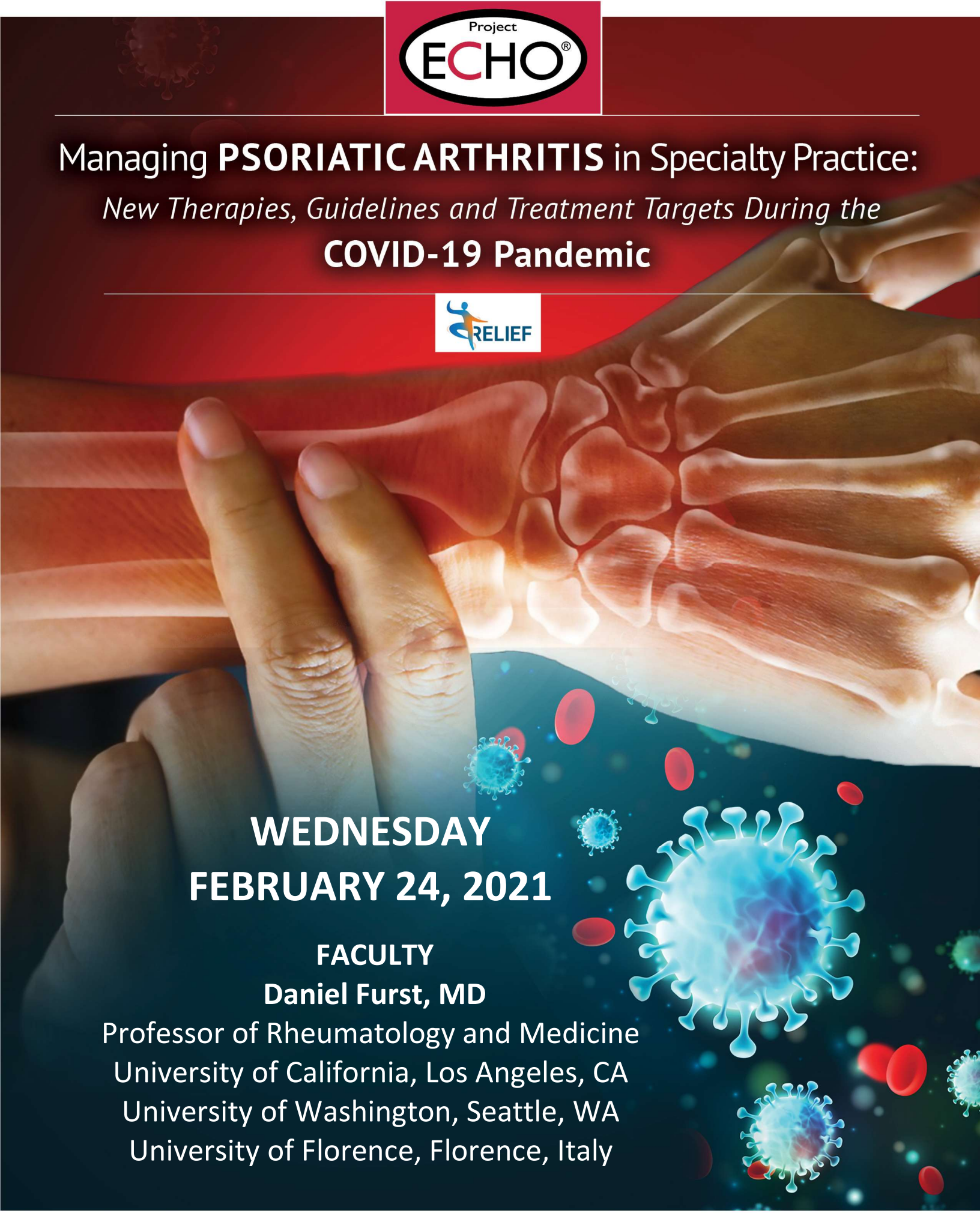
Project ECHO®

Managing **PSORIATIC ARTHRITIS** in Specialty Practice:

New Therapies, Guidelines and Treatment Targets During the **COVID-19 Pandemic**

RELIEF



WEDNESDAY
FEBRUARY 24, 2021

FACULTY

Daniel Furst, MD
Professor of Rheumatology and Medicine
University of California, Los Angeles, CA
University of Washington, Seattle, WA
University of Florence, Florence, Italy

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from Lilly.

The RELIEF Initiative
Managing Psoriatic Arthritis in Specialty Practice:
New Therapies, Guidelines and Treatment Targets During the COVID-19 Pandemic

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PROGRAM OVERVIEW
This case-based live virtual activity will cover the treatment and management of patients with psoriatic arthritis.

TARGET AUDIENCE
This activity is intended for rheumatologists and rheumatology advanced practice providers (NPs and PAs) who are involved in the care and treatment of patients with psoriatic arthritis.

Learning Objectives
- Identify the risk of COVID-19-related infections in PsA, along with their impact on therapeutic choice
- Pursue strategies to optimize PsA therapy in the COVID-19 era while minimizing risks and adverse events
- Assess methods for better evaluating and communicating with patients through telemedicine and virtual platforms
- Apply new ways to initiate and manage PsA treatment, monitor PsA disease progression and address adverse events via virtual communication

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NURSING CREDIT INFORMATION
Purpose: This program would be beneficial for nurses involved in the care of patients with psoriatic arthritis.
CNE Credits: 1.0 ANCC Contact Hour.

CNE ACCREDITATION STATEMENT
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CME Content Review
The content of this activity was independently peer-reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review
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1. Read the CME/CNE information and faculty disclosures.
2. Participate in the live virtual activity.
3. Submit the evaluation form to Med Learning Group.

You will receive your certificate upon completion as a downloadable file.

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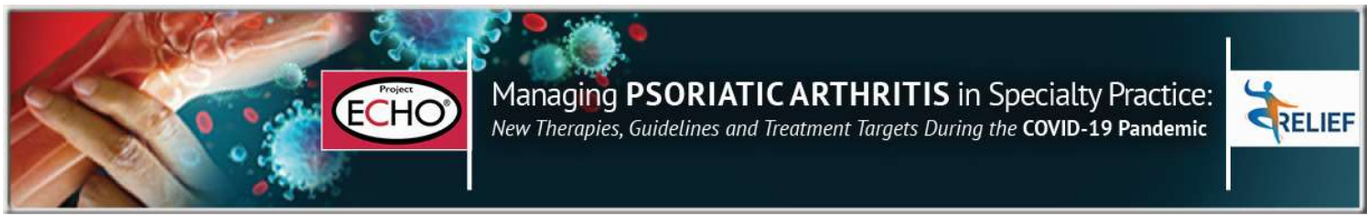

AGENDA

Introduction/Background

- Epidemiology and pathophysiology
- COVID-19 background
- COVID-19 and rheumatology: implications for assessment and evaluation
- Disease domains and joint manifestations
- Identification and diagnosis

Medical Management of PsA in the COVI-19 Era

- 2019 ACR guidelines and their application to practice
- Therapeutic considerations in COVID-19
- Conventional agents
- Biologics, small molecules:
    - Inhibitors of TNF, IL-12/23, IL-17A, IL-23, phosphodiesterase 4, T cell costimulation, and janus kinases
- Evolving standards of treatment in the COVID-19 era
- Treating-to-target: establishing goals of therapy

Telemedicine and Patient Considerations in the COVID-19 Pandemic

- Early diagnosis and initiation of treatment for long-term success
- Effect of management decisions on patient QoL
- Lowering disease burden (personal, societal, economic) through effective treatment
- Telemedicine: the changing face of rheumatology consults during the pandemic
- Case Study(s)

Conclusions and Q/A

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- During the course of this lecture, Dr Furst will discuss the use of medications for both FDA-approved and non-approved indications

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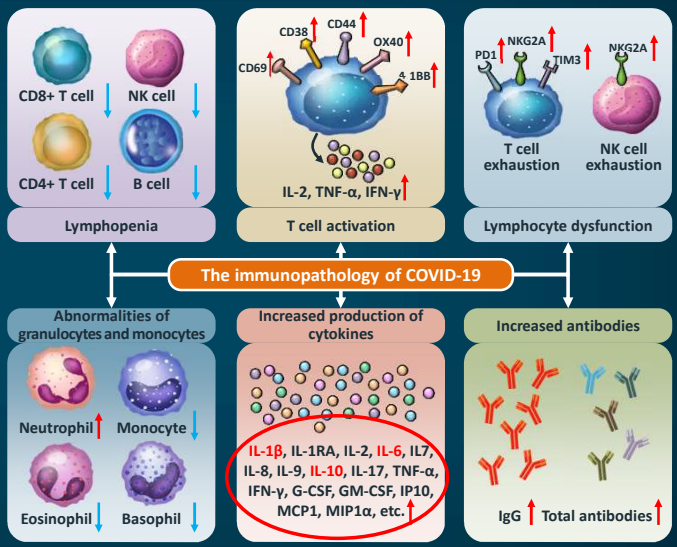
COVID-19-associated Hyperinflammation

- Clinical deterioration in COVID-19 often occurs 7-10 days after symptom onset when viral titres decline
  - Pathology likely driven by inflammation rather than direct viral injury
- Elevated inflammatory markers in COVID-19 patients are significantly associated with risk of next-day escalation of respiratory support or death (HR, 2.24)



Manson JJ, et al. *Lancet Rheumatol*. 2020;2:e594-e602. Yang L, et al. *Signal Transduct Target Ther*. 2020;5:128.

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Concerns During the COVID-19 Pandemic

- Patients with **PsA are not at increased risk of death, invasive ventilation, ICU admission, or serious complications from COVID-19**
  - Impact of PsA therapies on COVID-19 disease severity is unknown
- Risk of poor outcomes from COVID-19 appears to be related primarily to general risk factors such as age and comorbidities

Mortality in an Observational Study of COVID-19 Cases in China (n = 72,314)	
Characteristics	**Deaths (%)**
All confirmed cases	2.3
• Critical cases	49.0
• ≥80 years of age	14.8
• Cardiovascular disease	10.5
• 70-79 years of age	8.0
• Diabetes	9.2
• Chronic respiratory disease	8.0
• Hypertension	6.0
• Cancer	7.6

Conclusion: Increased % with age>=70 yrs, lung disease,CV/HBP, Diabetes, cancer

Mikuls TR, et al. *Arthritis Rheumatol*. 2020;72:1241-1251. Pablos JL, et al. *Ann Rheum Dis*. 2020;79:1544-1549. Wu Z, et al. JAMA. 2020;323:1239-1242. Wollina U, et al. *Dermatol Ther*. 2020;33:e13743.

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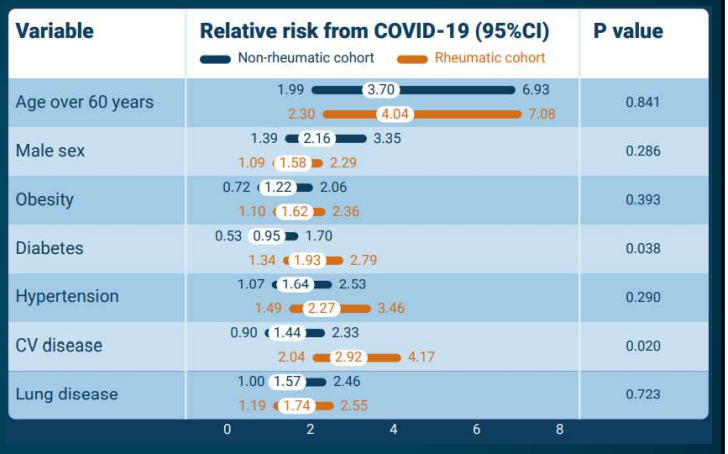
Impact of PsA Comorbidities on COVID-19 Outcomes

- PsA is associated with a higher incidence of CV disease, metabolic syndrome, obesity, diabetes, dyslipidemia, and inflammatory bowel disease
- Risk of poor outcomes for COVID-19 appears to be related to general risk factors such as older age, male sex, and comorbidities (obesity, diabetes, hypertension, CV or lung disease)



CV = cardiovascular; IBD = inflammatory bowel disease
Pablos JL, et al. *Ann Rheum Dis*. 2020;79:1544-1549.

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COVID-19 Treatment Modifications

Treatment of Rheumatic Disease in the Absence of COVID-19 Infection or Exposure	
HCQ/CQ, SSZ, MTX, LEF, immunosuppressants (tacrolimus, CSA, MMF, AZA), biologics, JAK inhibitors, NSAIDs	Continue therapy
Low-dose corticosteroids	May be started if clinically indicated (<10 mg prednisone equivalent/day)
Following SARS-CoV-2 Exposure	
HCQ/CQ, SSZ, NSAIDs	May be continued
Immunosuppressants (tacrolimus, CSA, MMF, AZA), non-IL-6 biologics, JAK inhibitors	Stop therapy temporarily, pending a negative COVID-19 test or 2 weeks of symptom-free observation
IL-6 inhibitors	May be continued in select circumstances
Documented or presumptive COVID-19	
HCQ/CQ	May be continued
SSZ, MTX, LEF, non-IL-6 biologics, immunosuppressants, and JAK inhibitors	Withhold or stop therapy
NSAIDs	Should be stopped in patients with severe respiratory symptoms

- All recommendations based on very low quality of evidence and moderate to high consensus
- Recommendations are for rheumatic disease in general and are not subdivided by patient disease. There are no specific recommendations for PsA.
  - May reinitiate therapy within 7-14 days of symptom resolution for those with mild COVID-19
  - Consider reinitiating therapy in 10-17 days after positive PCR results if asymptomatic COVID-19
  - Timing of reinitiating therapy after severe COVID-19 should be made on case-by-case basis

AZA = azathioprine; CSA = cyclosporine A; CQ = cloroquine; HCQ = hydroxychloroquine; IL = interleukin; JAK = Janus kinase; LEF = leflunomide; MMF = mycophenolate mofetil; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; SSZ = sulfasalazine

Mikuls TR, et al. *Arthritis Rheumatol*. 2020;72:1241-1251.

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Corticosteroid Use During the COVID-19 Pandemic

- A case series of 600 patients found prednisone >10 mg/day was associated with increased odds of hospitalization (OR, 2.05)
- A study in patients with inflammatory bowel disease and COVID-19 found steroids increase the risk of severe COVID-19 (aOR, 6.0)

Glucocorticoids should be used at the lowest possible dose to control rheumatic disease, regardless of exposure or infection status

Glucocorticoids should not be abruptly stopped, regardless of exposure or infection status

OR = odds ratio; aOR = adjusted odds ratio.

Gianfrancesco M, et al. *Ann Rheum Dis*. 2020;79:859-866. Brenner EJ, et al. *Gastroenterology*. 2020;159:481-491. Mikuls TR, et al. *Arthritis Rheumatol*. 2020;72:1241-1251.

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ACR COVID-19 Vaccination Guidance for Rheumatic Patients

Medication	Timing Considerations for Immunomodulatory Therapy and Vaccination
Hydroxychloroquine; IVIG; glucocorticoids, prednisone-equivalent dose <20mg/day	No modifications to either immunomodulatory therapy or vaccination timing
SSZ; LEF; MMF; AZA; Cyclophosphamide (oral); TNFi; IL-6R; IL-1; IL-17; IL-12/23; IL-23; Belimumab; oral calcineurin inhibitors; Glucocorticoids, prednisone-equivalent dose ≥20mg/day	No modifications to either immunomodulatory therapy or vaccination timing
Methotrexate	Hold MTX 1 week after each vaccine dose, for those with well-controlled disease; no modifications to vaccination timing
JAKi	Hold JAKi for 1 week after each vaccine dose; no modification to vaccination timing
Abatacept SQ	Hold SQ abatacept both one week prior to and one week after the first COVID-19 vaccine dose (only); no interruption around the second vaccine dose
Abatacept IV	Time vaccine administration so that the first vaccination will occur four weeks after abatacept infusion (i.e., the entire dosing interval), and postpone the subsequent abatacept infusion by one week (i.e., a 5-week gap in total); no medication adjustment for the second vaccine dose
Cyclophosphamide IV	Time CYC administration so that it will occur ~1 week after each vaccine dose, when feasible
Rituximab	Assuming that patient's COVID-19 risk is low or is able to be mitigated by preventive health measures (e.g., self-isolation), schedule vaccination so that the vaccine series is initiated approximately 4 weeks prior to next scheduled rituximab cycle; after vaccination, delay RTX 2-4 weeks after 2nd vaccine dose, if disease activity allows

ACR COVID-19 Vaccine Clinical Guidance Summary. Available at: https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf.

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Incorporating Telehealth into Your Practice

- **Schedule enough time**. Telehealth consults often take longer than expected to find the required information
- **Train staff in triaging symptom burden**. Identify patients with unstable symptoms who require an in-person appointment
- **Educate on self-management**. Patients may not come in for a follow-up appointment for weeks or months.
  - Teach about warning signs that require prompt evaluation
  - Educate about how to manage symptoms remotely
  - Ensure patients have enough medication
- **Clarify expectations** of what can or cannot be done remotely
  - Recognize patients who require in-person evaluation

Centers for Disease Control and Prevention website (https://www.cdc.gov/coronavirus/2019-ncov/hcp/telehealth.html). Landewe RBM, et al. *Ann Rheum Dis.* 2020;79:851-858.

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Strategies to Increase Telehealth Uptake

- **Use technology** that allows you to send and receive patient-reported outcomes scales
- **Prescreen patients with disease activity scales** and request in-person visit if scores are high
- **Offer flexibility** in platforms that can be used for video consultation, and non-video options to serve patients with limited technology and connectivity
- **Postpone** regular blood monitoring and face-to-face consultations in patients with stable disease and therapy without signs of drug toxicity
- **Communicate with insurers/payers** to understand availability of covered telehealth services

Centers for Disease Control and Prevention website (https://www.cdc.gov/coronavirus/2019-ncov/hcp/telehealth.html). Landewe RBM, et al. *Ann Rheum Dis*. 2020;79:851-858.

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Treatment Options

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Initiating Therapy

Treatment-naïve Active PsA

Discuss with the patient, since all recommendations are conditional based on low to very low quality evidence

Start TNFi biologic over OSM, IL-17i biologic or IL-12/23i biologic May consider alternative choices in some situations	Start OSM over IL-17i biologic or IL-12/23i biologic May consider alternative choices in some situations	Start MTX over NSAIDs May consider alternative choices in some situations	Start IL-17i biologic over IL-12/23i biologic May consider alternative choices in some situations

- Contraindications to TNFi include congestive heart failure, previous serious infection, recurrent infections,or demyelinating disease
- An OSM (MTX, SSZ, LEF, CSA, or APR) may be considered if disease is not severe, oral therapy is preferred, or patient does not want to start a biologic

APR = apremilast; CSA = cyclosporine; IL = interleukin; LEF = leflunomide; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; OSM = oral small molecule; SSZ = sulfasalazine; TNFi = tumor necrosis factor-alpha inhibitor.

Singh JA, et al. *Arthritis Rheumatol.* 2019;71:5-32.

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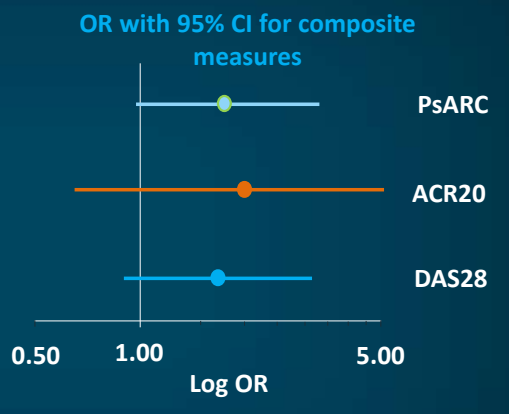
Methotrexate Is Not a DMARD in PsA

- 6-month DBRCT of MTX 15 mg/week vs PBO
- Primary outcome: PsARC
  Secondary outcomes: ACR20, DAS28, global and skin scores
- No difference in SJC, TJC, CRP/ESR, PsARC, ACR20, DAS28 at 3 and 6 months
- Patient, MD global, and skin scores significantly improved at 6 months (*P*=0.01, 0.02, 0.02)



Despite issues with study design, MTX does not have disease-remitting properties.

CRP = C-reactive protein; DBRCT = double-blind, randomized controlled trial; ESR = erythrocyte sedimentation rate; MTX = methotrexate; PBO = placebo; PsARC = PsA response criteria; DAS = Disease Activity Score; SJC = swollen joint count; TJC = tender joint count.

Kingsley GH, et al. *Rheumatology (Oxford).* 2012;51:1368-1377.

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CSA in Psoriasis and PsA

- CSA 2.5-5 mg/kg/day yielded PASI75 response in 28% to 97% of patients
- Remission could be maintained at CSA dose of at least 3mg/kg/day
- More than 50% of patients treated with CSA may have an increase in serum creatinine value >30% of baseline if treatment is prolonged for 2 years

24 Week Randomized Open NSAID* Controlled Study of Cyclosporin A in PsA (N=99)

	P-value	Significance CSA vs NSAID*
ACR50	0.02	+
ACR70	0.05	+
Swollen Joint Count	0.05	+
Tender Joint Count	0.01	+
Pain	0.002	+
Patient Global improved ≥1 point	0.04	+
MD Global improved ≥1 point	0.01	+

*NSAID +/- prednisone 5 mg daily +/- analgesics

Salvanarani C, et al. *J Rheum*. 2001;28:2274-2282. Maza J-H, et al. *JEADV*. 2011;25(2):19-27.

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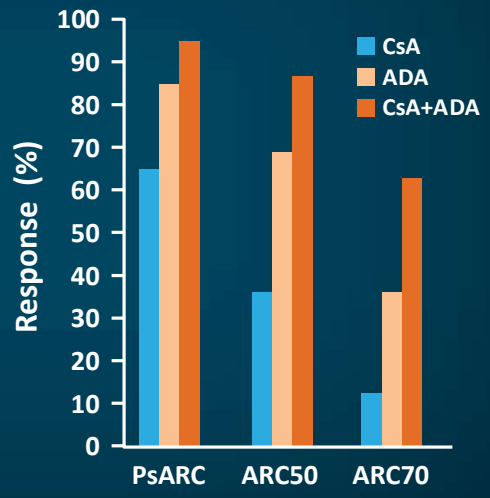
Adalimumab Or Cyclosporine as Monotherapy or Combination For Severe PsA: A Prospective, 12-month, Observational Study

- A 12-month, observational study of 170 TNFi- and cyclosporine-naïve patients
- Patients who received adalimumab (40mg Q2W) (n=57), cyclosporine (2.5-3.75 mg/kg/day) (n=58), or their combination (n=55)
- MTX-IR (25 mg weekly or less, for a minimum of 6 months)
- Assessments: 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 months
- Combination therapy improved PASI50 response rates but NOT beyond the effect of cyclosporine monotherapy (not shown)



MTX-IR = methotrexate inadequate response
Karanikolas GN, et al. *J Rheumatol*. 2011;38:2466-2474.

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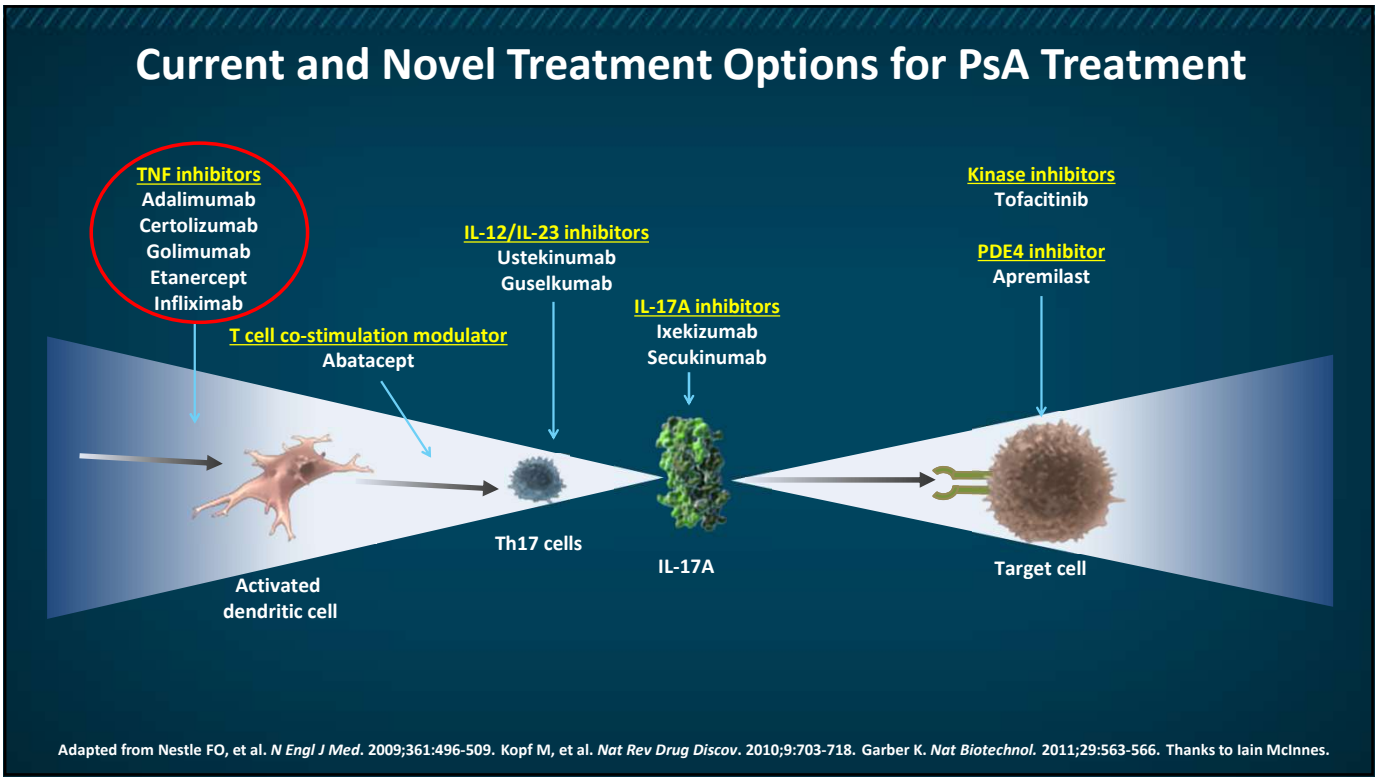
Current and Novel Treatment Options for PsA Treatment
TNF inhibitors
Adalimumab
Certolizumab
Golimumab
Etanercept
Infliximab
T cell co-stimulation modulator
Abatacept
IL-12/IL-23 inhibitors
Ustekinumab
Guselkumab
IL-17A inhibitors
Ixekizumab
Secukinumab
Kinase inhibitors
Tofacitinib
PDE4 inhibitor
Apremilast
Activated dendritic cell
Th17 cells
IL-17A
Target cell
Adapted from Nestle FO, et al. N Engl J Med. 2009;361:496-509. Kopf M, et al. Nat Rev Drug Discov. 2010;9:703-718. Garber K. Nat Biotechnol. 2011;29:563-566. Thanks to Iain McInnes.

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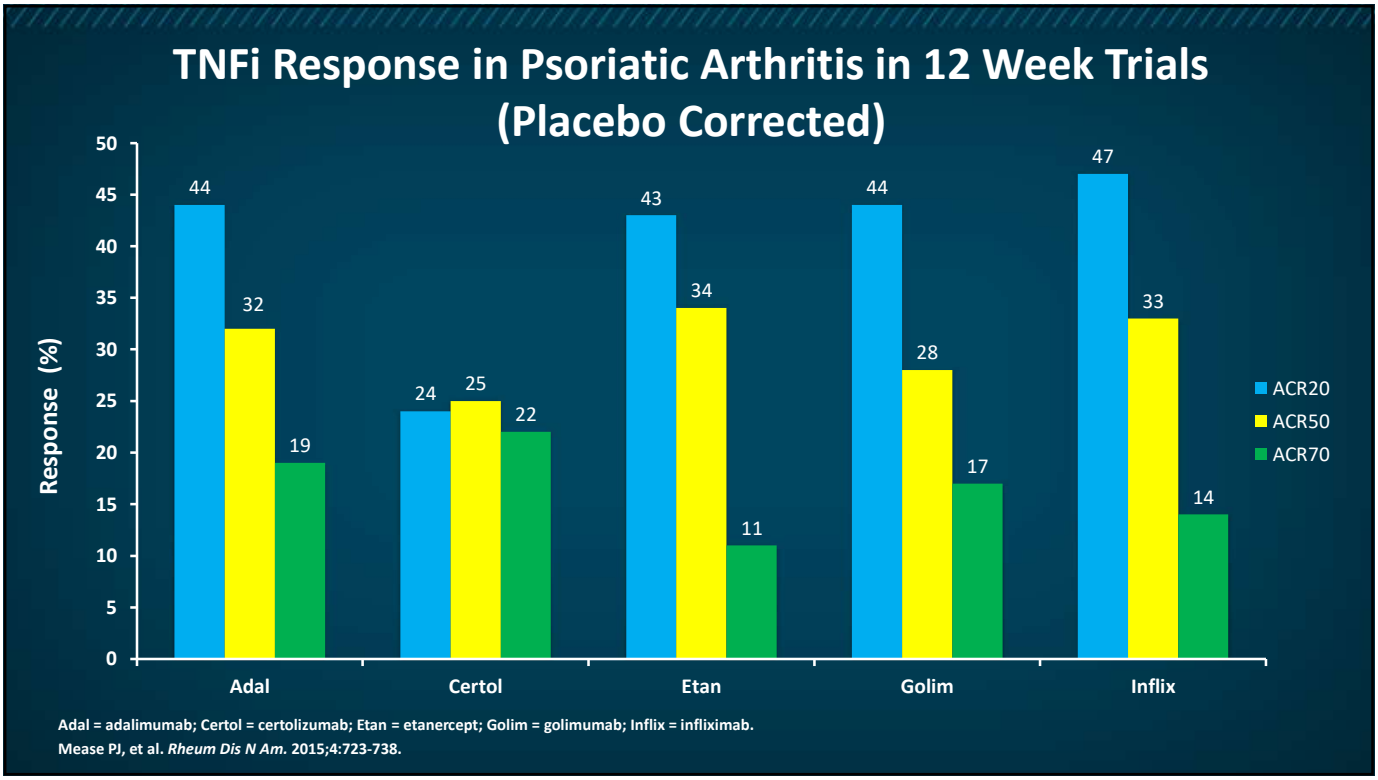
TNFi Response in Psoriatic Arthritis in 12 Week Trials (Placebo Corrected)
Response (%)
50
45
40
35
30
25
20
15
10
5
0
44
32
19
24
25
22
43
34
11
44
28
17
47
33
14
Adal
Certol
Etan
Golim
Inflix
ACR20
ACR50
ACR70
Adal = adalimumab; Certol = certolizumab; Etan = etanercept; Golim = golimumab; Inflix = infliximab.
Mease PJ, et al. Rheum Dis N Am. 2015;4:723-738.

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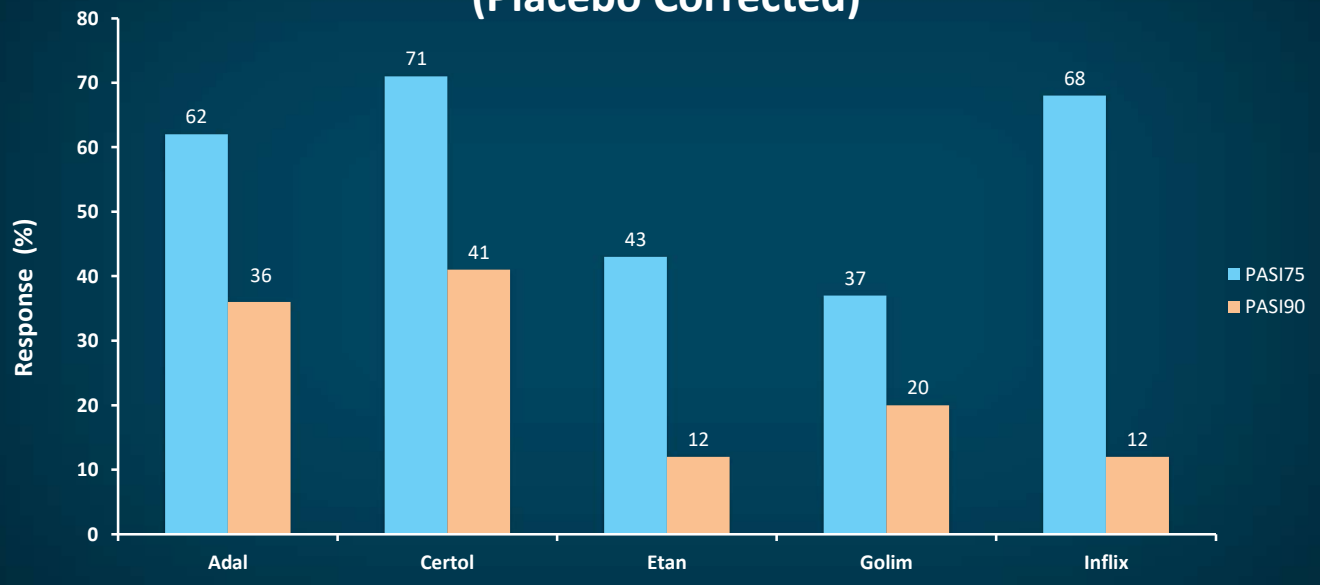
TNFi Response in Psoriasis in 12 Week Trials (Placebo Corrected)



Adal = adalimumab; Certol = certolizumab; Etan = etanercept; Golim = golimumab; Inflix = infliximab.

Mease PJ, et al. *Rheum Dis Clin N Am*. 2015;4:723-738. Yang H, et al. *Health Tech Assess.* 2011;15(1):87-95. Reich K, et al. *Br J Derm.* 2012;167:180-190.

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Anti-TNFs in PsA: Additional Outcomes

- Enthesitis: ~60–75% improvement
  - Assessment methods evolving: 4-point, MASES, Leeds, SPARCC
- Dactylitis: ~60% improvement
  - Assessment methods evolving: count, score, Leeds dactylometer
- Function
  - Significant improvement achieved as assessed by HAQ
- QoL
  - Significant improvements in SF-36, PsAQoL, DLQI, EQ-5D
- Fatigue
  - Significant improvement observed (eg, FACIT)

MASES = Maastricht Enthesitis Index; SPARCC = Spondyloarthritis Research Consortium of Canada; PsAQoL = PsA quality of life; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-domain; FACIT = Functional Assessment of Chronic Illness Therapy.

Mease PJ. *Ann Rheum Dis*. 2011;70(1):i77-i84. Mease PJ. *Arthritis Care Res (Hoboken)*. 2011:63(11):S64-S85.

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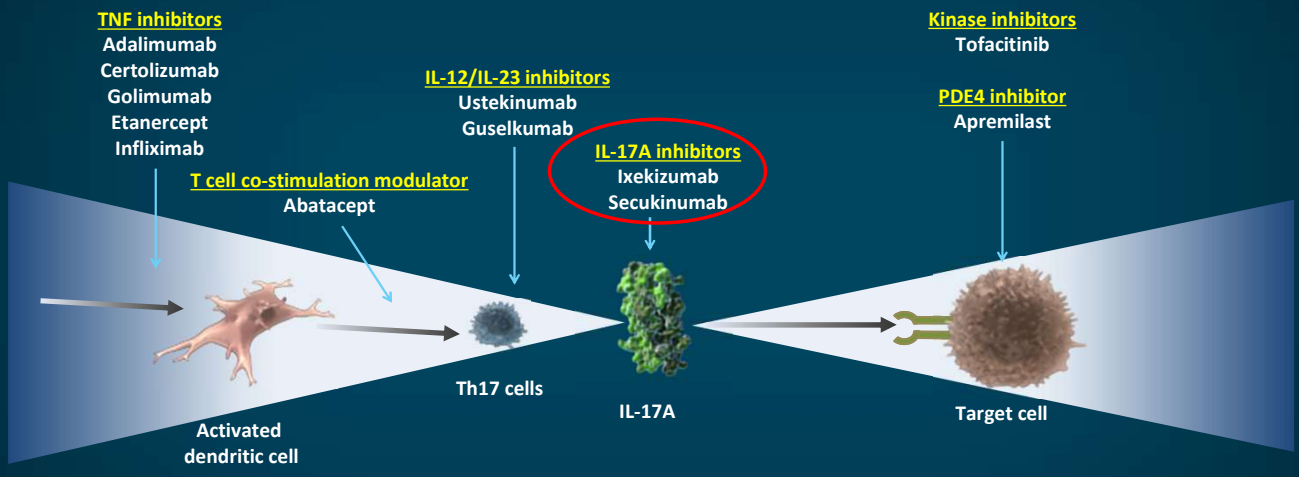
Current and Novel Treatment Options for PsA Treatment



Adapted from Nestle FO, et al. *N Engl J Med*. 2009;361:496-509. Kopf M, et al. *Nat Rev Drug Discov*. 2010;9:703-718. Garber K. *Nat Biotechnol.* 2011;29:563-566. Thanks to Iain McInnes.

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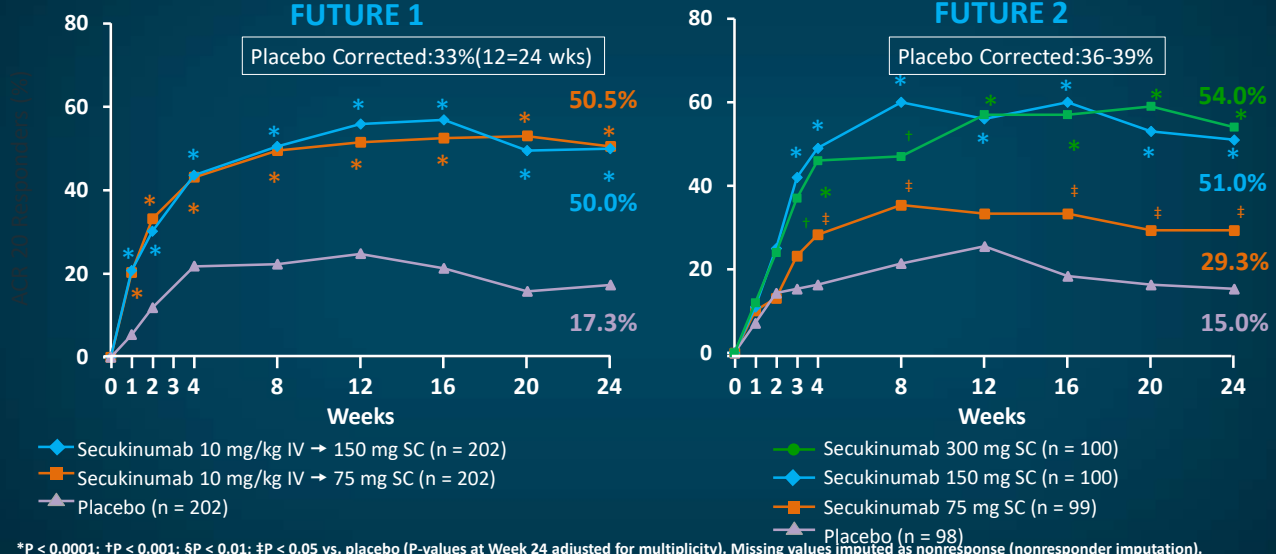
Secukinumab in PsA

ACR20: Primary Outcome Measure



*P < 0.0001; †P < 0.001; §P < 0.01; ‡P < 0.05 vs. placebo (P-values at Week 24 adjusted for multiplicity). Missing values imputed as nonresponse (nonresponder imputation).
IV =intravenous; SC = subcutaneous.
Mease PJ, et al. *N Engl J Med.* 2015;373:1329-1339. McInnes IB, et al. *Lancet.* 2015;386:1137-1146.

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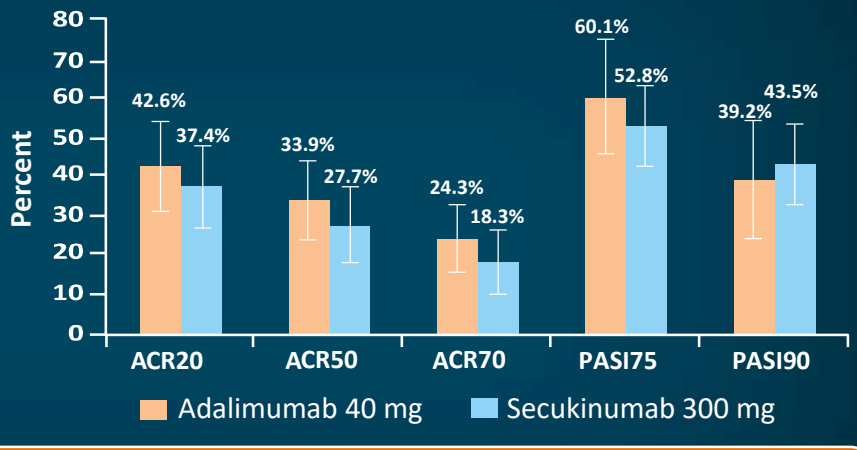
Adalimumab vs Secukinumab in PsA: Indirect Comparison

- N = 302 patients from ADEPT (ADA) and 2 PsA trials of SEC (FUTURE 1 & 2)
- Matching for age, weight, gender, race, MTX use, PASI, dactylitis, enthesitis, HAQ-DI
- Number needed to treat to achieve 1 additional PASI75 responder:
  - ADA 40 mg: 1.7
  - SEC 150 mg: 2.2
  - SEC 300 mg: 1.9



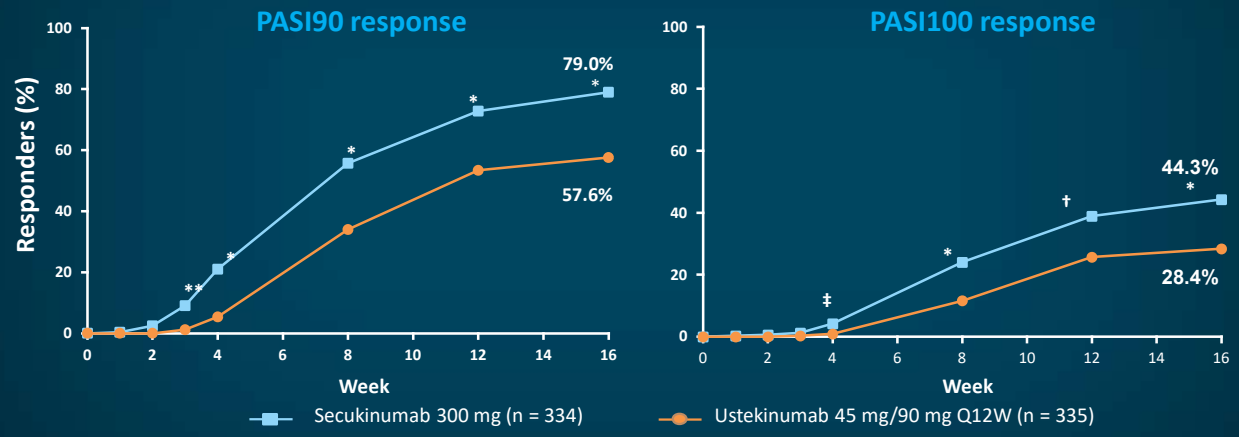
Conclusion: Secukinumab (anti-IL-17) was shown to be as effective or slightly less effective than adalimumab for PsA (numerical only).

ADA = adalimumab; SEC = secukinumab.

Betts KA, et al. *Arthritis Rheumatol.* 2015;67(10): Abstract 2868. Strand V. *Rheumatol Ther.* 2017;4:349-362.

25

CLEAR Study: Secukinumab (aIL-17A) vs Ustekinumab (aIL-12/23) in Psoriasis



Missing data were imputed as nonresponse; only response-evaluable patients were included.

**P*<0.0001; ***P*=0.0001; †*P*<0.001; ‡P<0.05

Thaci D, et al. *JAAD.* 2015;73(3):400-409.

26

Secukinumab: Adverse Events

Common Adverse Events[1]			
	SEC 300 mg	SEC 150 mg	Placebo
URTI	4 (4%)	8 (8%)	7 (7%)
Nasopharyngitis	6 (6%)	4 (4%)	8 (8%)
Diarrhea	2 (2%)	2 (2%)	3 (3%)
Headache	7 (7%)	4 (4%)	4 (4%)
Nausea	3 (3%)	4 (4%)	4 (4%)
Sinusitis	1 (1%)	2 (2%)	1 (1%)
Psoriatic arthropathy	0	3 (3%)	2 (2%)
Urinary tract infection	2 (2%)	4 (4%)	4 (4%)
Hematuria	2 (2%)	3 (3%)	1 (1%)
Vomiting	2 (2%)	2 (2%)	1 (1%)

Warnings[2]

1. Infection
2. Tuberculosis
3. Hypersensitivity reactions
4. **New or worsening inflammatory bowel disease**

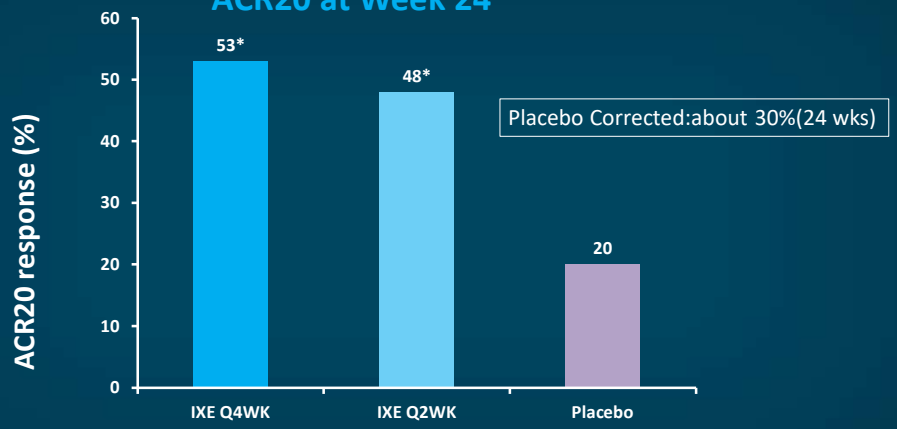
URTI = upper respiratory tract infection.

1. McInnes IB, et al. *Lancet*. 2015;386:1137-1146. 2. Secukinumab (Cosentyx®) PI 2017 (www.pharma.us.novartis.com/sites/www.pharma.us. novartis.com/files/cosentyx.pdf).

27

SPIRIT-P2: Ixekizumab in Patients with Active PsA and an Inadequate Response to TNFi

ACR20 at Week 24



Both the 2-week and 4-week ixekizumab dosing regimens improved the signs and symptoms of patients with active PsA who had an inadequate response to TNFi therapy.

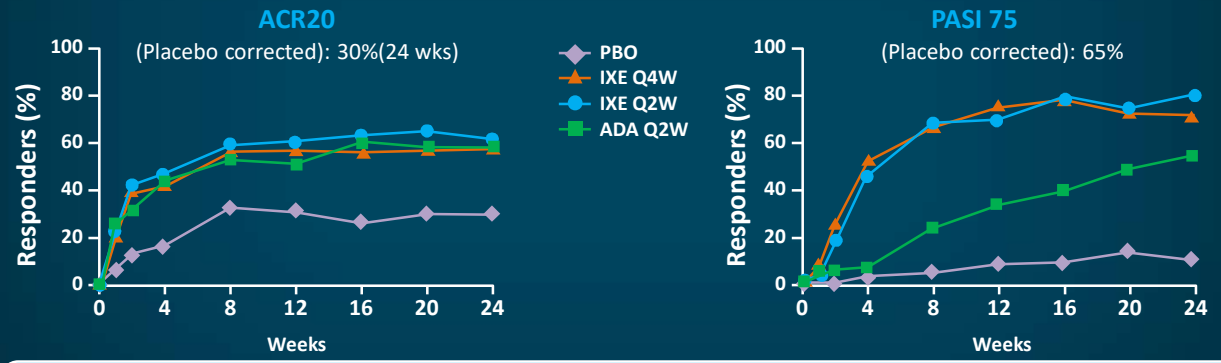
*P<0.0001 vs placebo
IXE = ixekizumab.

Nash P, et al. *Lancet*. 2017;389:2317-2327.

28

Ixekizumab vs Adalimumab for PsA

- Randomized, double-blind placebo-controlled trial in patients who were biologic DMARD naïve
- More patients achieved an ACR20 response with IXE Q2W (62.1%) or IXE Q4W (57.9%) than placebo (30.2%)
- Disease activity and functional disability were significantly improved with ixekizumab vs placebo (*P*< .01), and there was significantly less progression of structural damage at week 24 with ixekizumab (*P*< .01)

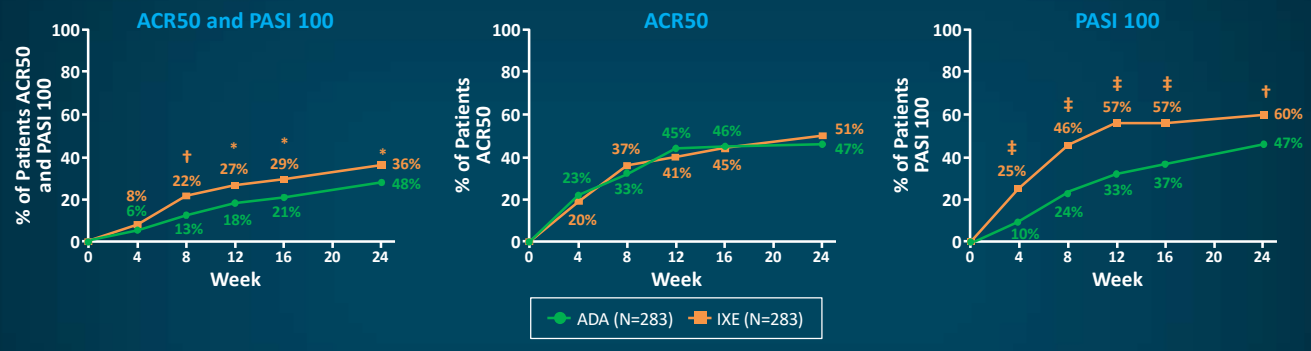


Conclusion: Ixekizumab and adalimumab were both equally better than placebo in PsA. Ixekizumab was better than adalimumab for psoriasis.

Mease P, et al. *Ann Rheum Dis*. 2017;76:79-87.

29

SPIRIT H2H: Head-to-Head Comparison of Ixekizumab and Adalimumab



- Ixekizumab was superior to adalimumab in achievement of simultaneous improvement in joint and skin disease (ACR50 and PASI 100) in patients with active PsA and inadequate response to csDMARDs
- Ixekizumab was non-inferior to adalimumab for ACR50 response (IXE: 51%, ADA: 47%) but superior for PASI 100 response (IXE: 60%, ADA:47%, *P*= .001)

Mease PJ, et al. *Ann Rheum Dis.* 2020;79:123-131.

csDMARD = conventional synthetic DMARD

30

Ixekizumab: Adverse Events

Ixekizumab Adverse Events		
	IXE 80 mg (n=1167)	Placebo (n=791)
Injection site reactions	196 (17%)	26 (3%)
Upper respiratory tract infections	163 (14%)	101 (13%)
Nausea	23 (2%)	5 (1%)
Tinea infections	17 (2%)	1 (<1%)

Adverse events occurring in ≥ 1% of IXE group, and more frequently than placebo.

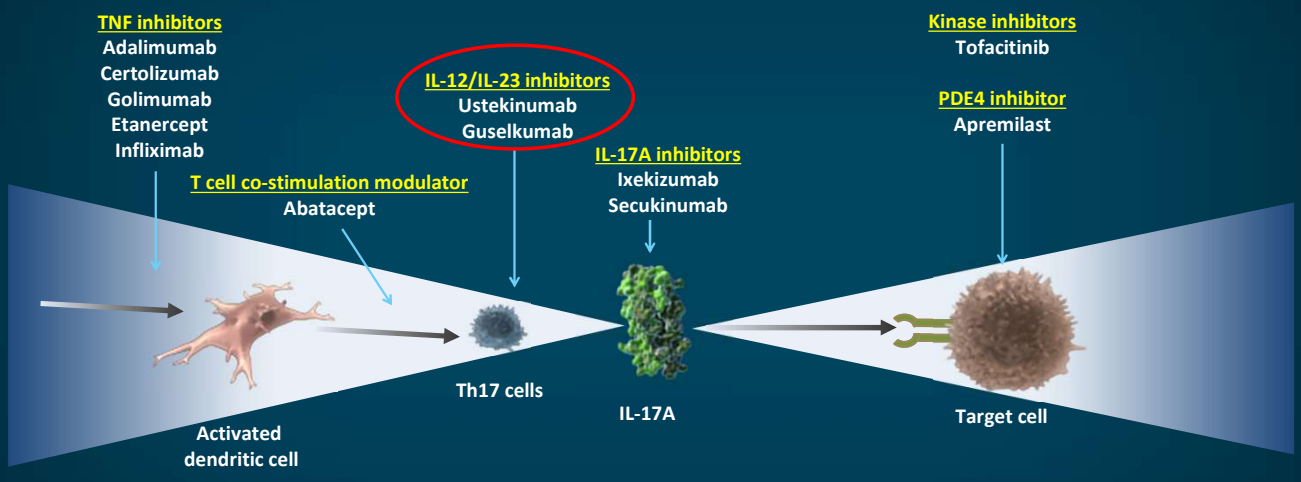
Warnings

1. Infection
2. Tuberculosis
3. Hypersensitivity reactions
4. Inflammatory bowel disease

Ixekizumab (Taltz®) prescribing information (https://pi.lilly.com/us/taltz-uspi.pdf)

31

Current and Novel Treatment Options for PsA Treatment



Adapted from Nestle FO et al. *N Engl J Med*. 2009;361:496-509. Kopf M et al. *Nat Rev Drug Discov*. 2010;9:703-718. Garber K. *Nat Biotechnol.* 2011;29:563-566. Thanks to Iain McInnes.

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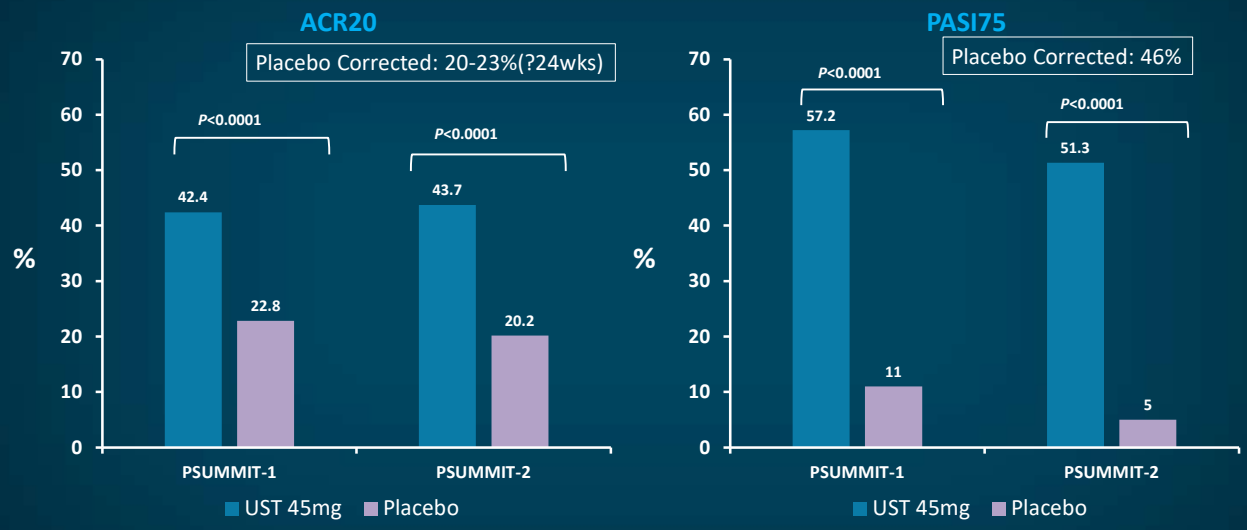
Ustekinumab: Efficacy in PsA



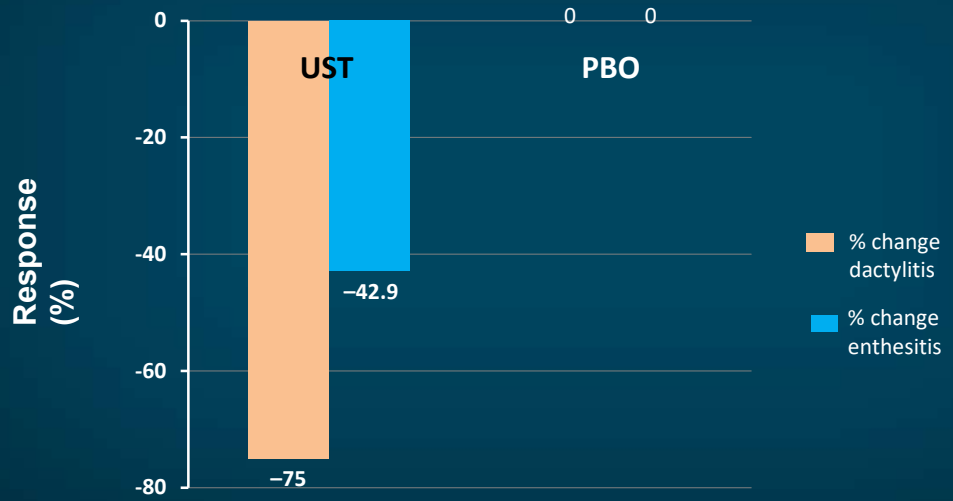
UST = ustekinumab.

McInnes IB et al. *Lancet.* 2013;382:780-789. Ritchlin C et al. *Ann Rheum Dis.* 2014;73:990-999.

33

Ustekinumab Is Effective in PsA

24-Week DBRCT
(PBO: n = 206; UST: n = 205; 45 mg IV at 0, 4, and every 12 weeks)



McInnes IB ,et al. *Ann Rheum Dis.* 2012;71(3):107. McInnes I. *Lancet.* 2013;382:780-789.

34

Ustekinumab Adverse Events

- Meta-analysis of 9626 patients in 30 RCT of 16 weeks duration
- AEs and SAEs include infections, cough, headache, upper respiratory tract infection, nausea, injection site reactions, CV event, cancer, and death

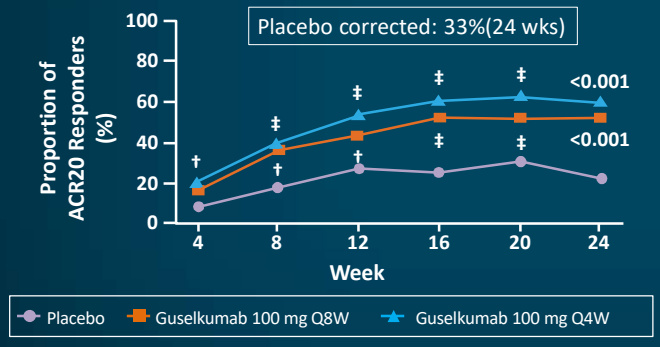
Adverse events	UST	Placebo	P value
Infections	1210 (19.7%)	588 (17.1%)	<0.01
Nasopharyngitis	318 (5.2%)	162 (4.7%)	0.31
Cough	21 (2.3%)	25 (4.8%)	0.01
Upper respiratory tract infection	150 (3.2%)	201 (7.1%)	<0.001
Nausea	113 (4.8%)	58 (5.0%)	0.80
Headache	302 (6.1%)	141 (5.1%)	0.06
Infusion/Injection site reaction	149 (3.9%)	44 (2.0%)	<0.001
Malignancy	3 (0.1%)	5 (0.2%)	0.16
Death	5 (0.1%)	1 (0.1%)	0.43
CV	7 (0.2%)	4 (0.2%)	1.00

Rolston VS, et al. *Dig Dis Sci*. 2020. doi:10.1007/s10620-020-06344-w.

35

DISCOVER-1 Trial of Guselkumab

- Phase 3, placebo-controlled trial of guselkumab in 381 patients with active PsA who were biologic-naïve or had previously received a TNFi
- 31% of patients had been previously treated with ≤2 TNFi agents



	Guselkumab 100 mg		Placebo
	Q4W	Q8W	
Number of patients	128	127	126
ACR20 response at week 24, n/N (%)			
Patients with prior TNFi use	22/38 (57.9%)	23/41 (56.1%)	7/39 (17.9%)
% difference vs. placebo (95% CI)	40.0 (20.8, 59.2)	38.5 (19.3, 57.7)	
Unadjusted p value	<0.001	<0.001	
Patients with inadequate response to prior TNFi	11/17 (64.7%)	9/15 (60.0%)	3/12 (25.0%)
% difference vs. placebo (95% CI)	42.4 (11.0, 73.9)	35.9 (0.8, 71.0)	
Patients without prior TNFi use	54/90 (60.0%)	43/86 (50.0%)	21/87 (24.1%)
% difference vs. placebo (95% CI)	35.9 (22.3, 49.4)	25.9 (12.0, 39.7)	
Unadjusted p value	<0.001	<0.001	

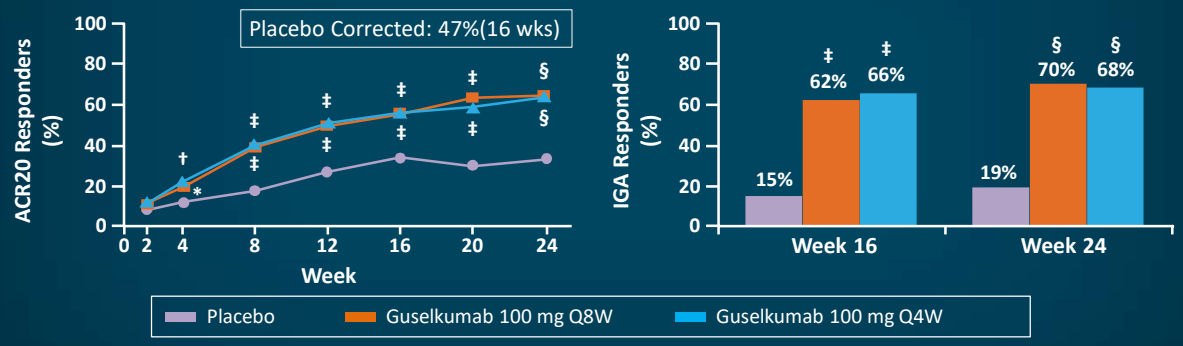
- ACR20 at week 24 was achieved by significantly greater proportions of patients in the guselkumab Q4W (59%) and Q8W (52%) groups than in the placebo group (22%)

Deodhar A, et al. Lancet. 2020;395:1115-1125.

36

DISCOVER-2 Trial of Guselkumab

- Phase 3 trial of 741 biologic-naïve patients with active PsA
- Patients randomized to guselkumab Q4W, Q8W, or placebo



- Significantly greater proportions of patients in the guselkumab Q4W (64%) and Q8W (64%) groups achieved ACR20 at week 24 than placebo (33%)

Mease PJ, et al. *Lancet*. 2020;395:1126-1136.

37

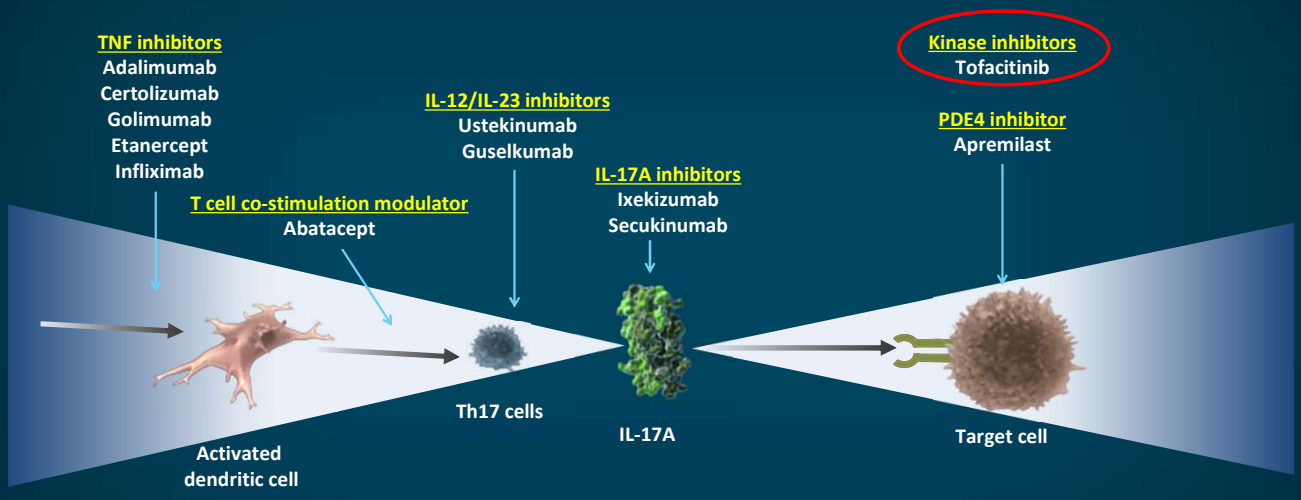
Guselkumab Adverse Events

	PBO	GUS	
		100 mg Q8W	100 mg Q4W
Patients with ≥1 AE (%)	60%	54%	55%
SAE (%)	4%	3%	0%
Discontinuation due to AE (%)	2%	2%	1%
Infections (%)	25%	26%	24%
Alanine aminotransferase increase	2%	6%	4%
Aspartate aminotransferase increase	2%	7%	2%
Nasopharyngitis	6%	13%	5%
Upper respiratory tract infection	6%	6%	9%

Deodhar A, et al. *Lancet*. 2020;395:1115-1125.

38

Current and Novel Treatment Options for PsA Treatment



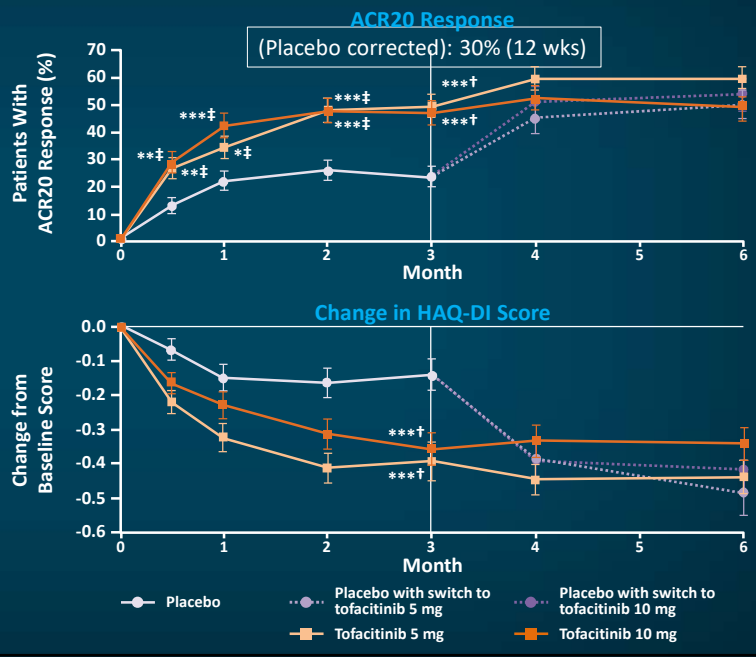
Adapted from Nestle FO et al. *N Engl J Med*. 2009;361:496-509. Kopf M et al. *Nat Rev Drug Discov*. 2010;9:703-718. Garber K. *Nat Biotechnol.* 2011;29:563-566. Thanks to Iain McInnes.

39

Efficacy of Tofacitinib in PSA

- 395 patients with active PsA and an inadequate response to TNFi were randomized to:
  - Tofacitinib 5 mg BID
  - Tofacitinib 10 mg BID
  - Placebo, with a switch to 5 mg or 10 mg tofacitinib BID at 3 months
- No efficacy noted on Leeds Enthesitis Index, Dactylitis Severity Score, FACIT-F total score, and SF-36 physical functioning

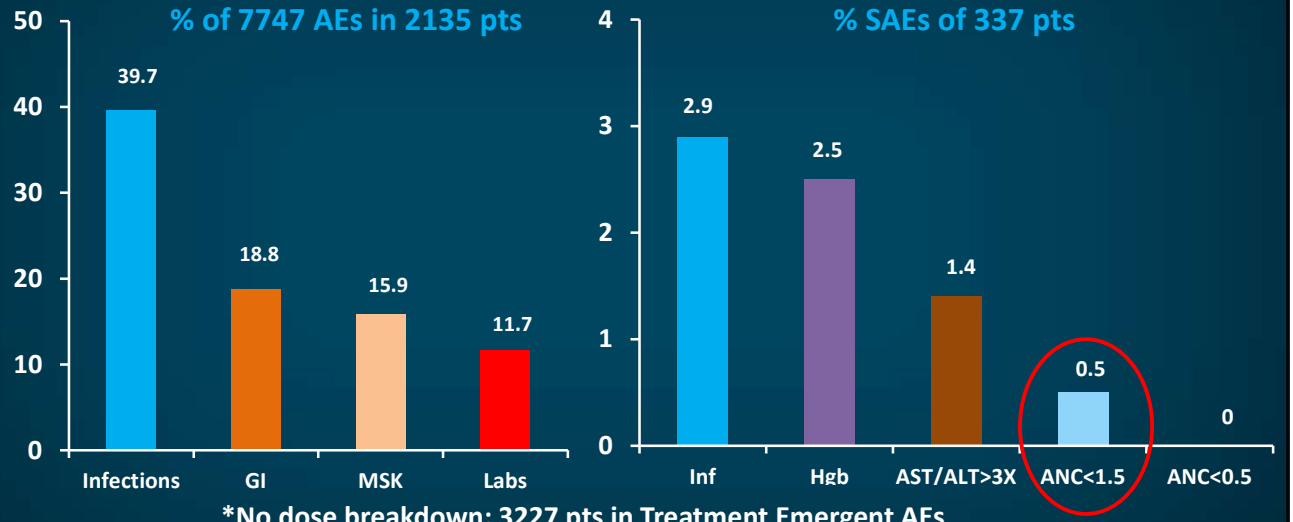
Conclusion: Tofacitinib has some efficacy in PsA, but no efficacy noted in some symptoms



Gladman D, et al. *N Eng J Med*. 2017;377:1525-1536.

40

Adverse Events in 3118 Patient-Years in Tofacitinib Open-Label, Long-Term Extension Study of Therapy for RA*



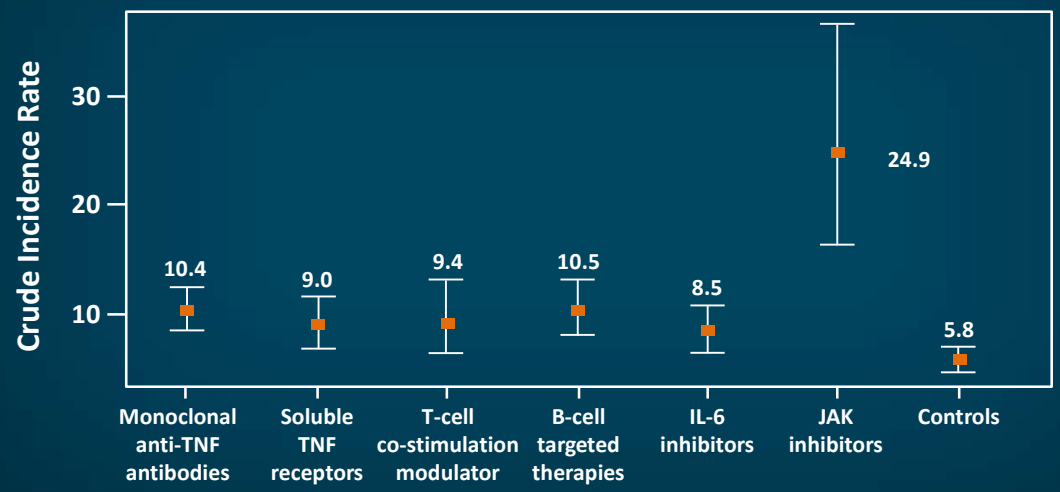
*No dose breakdown; 3227 pts in Treatment Emergent AEs

GI = gastrointestinal disorders; MSK = musculoskeletal and connective tissue disorders; Inf = infections; HGB = decreased hemoglobin; AST/ALT = aspartate/alanine; ANC = absolute neutrophil count.

Wollenhaupt J ,et al. ACR 2011. Abstract 407.

41

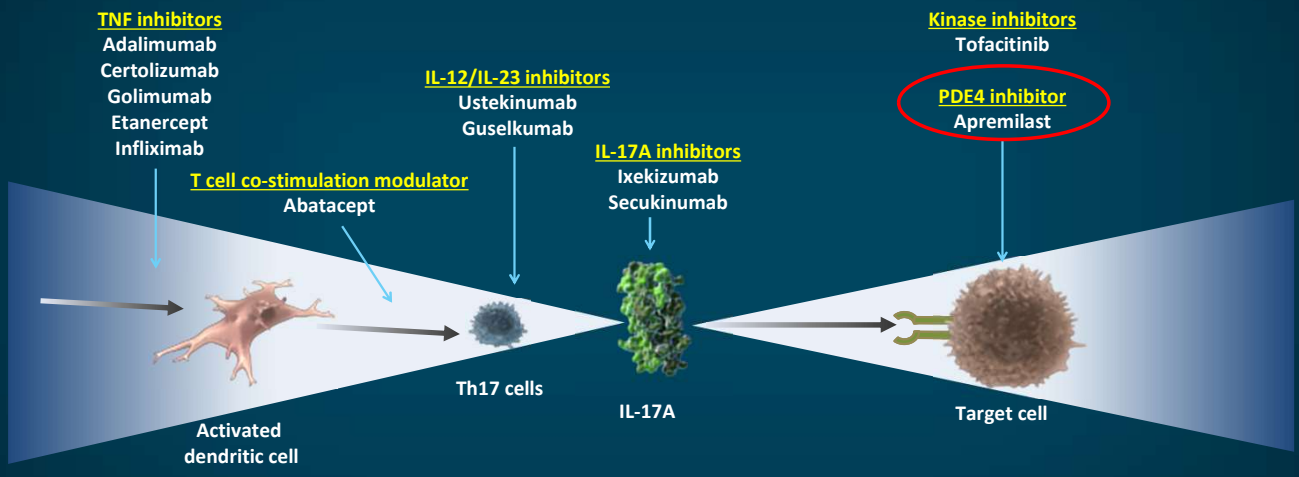
Incident Rates of Herpes Zoster in RA Patients



Strangfeld A, et al. EULAR 2020. Abstract OP0238.

42

Current and Novel Treatment Options for PsA Treatment



Adapted from Nestle FO et al. *N Engl J Med*. 2009;361:496-509. Kopf M et al. *Nat Rev Drug Discov*. 2010;9:703-718. Garber K. *Nat Biotechnol.* 2011;29:563-566. Thanks to Iain McInnes.

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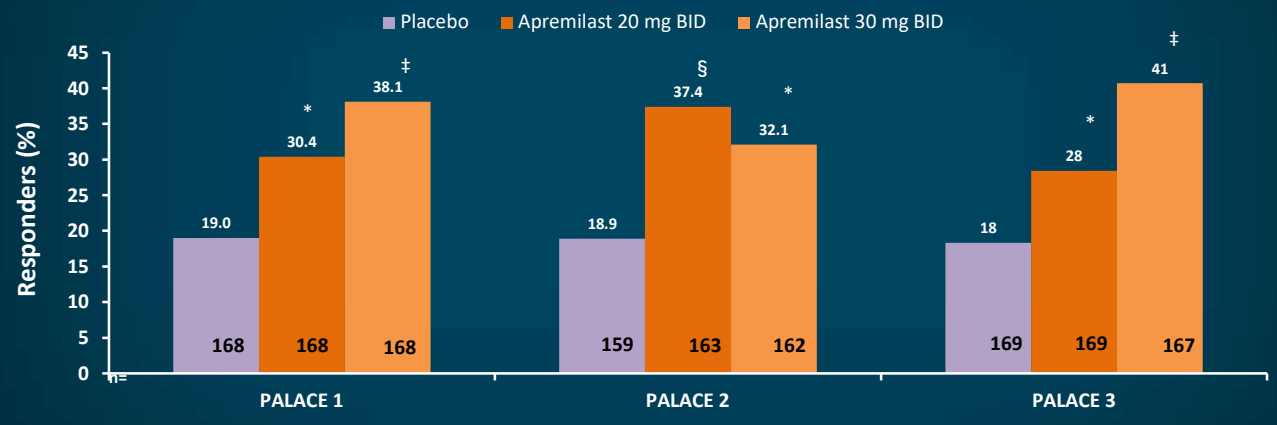
Apremilast in PsA: PALACE 1, 2, and 3

Primary endpoint across studies: ACR20 response at week 16

ITT population (NRI)

Placebo Correct3ed Resoinse:15-23%(16 wks)



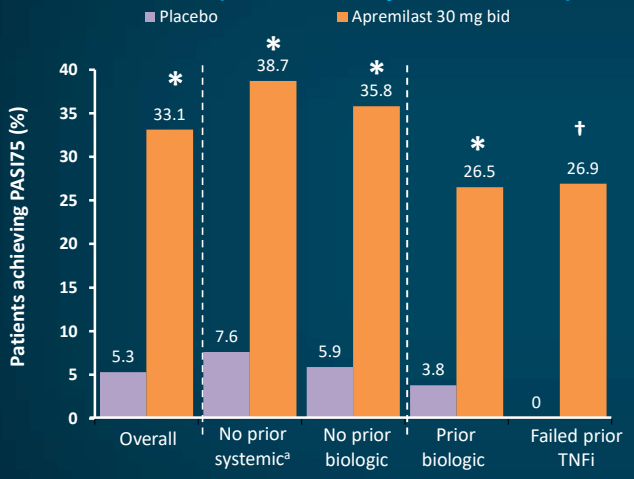
*P<0.05; §P<0.005; ‡P≤0.0001 vs placebo.
NRI = non-responder imputation

Kavanaugh A, et al. *Ann Rheum Dis.* 2014;73:1020-1026. Cutolo M, et al. *J Rheumatol.* 2016;43:1724-1734. Edwards CJ, et al. *Ann Rheum Dis.* 2016;75:1065-1073.

44

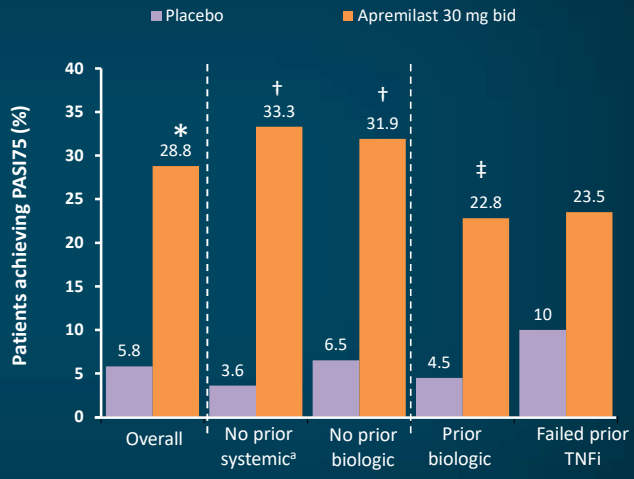
Apremilast in Moderate-to-Severe Psoriasis

ESTEEM 1: PASI75 by prior treatment at week 16 (LOCF, full analysis set; N = 844)



*P<0.0001; †P=0.0273 vs PBO; [a]Conventional ± biologics

ESTEEM 2: PASI75 by prior treatment at Week 16 (LOCF, full analysis set; N = 411)



*P<0.0001; †P<0.001, ‡P=0.0069 vs PBO

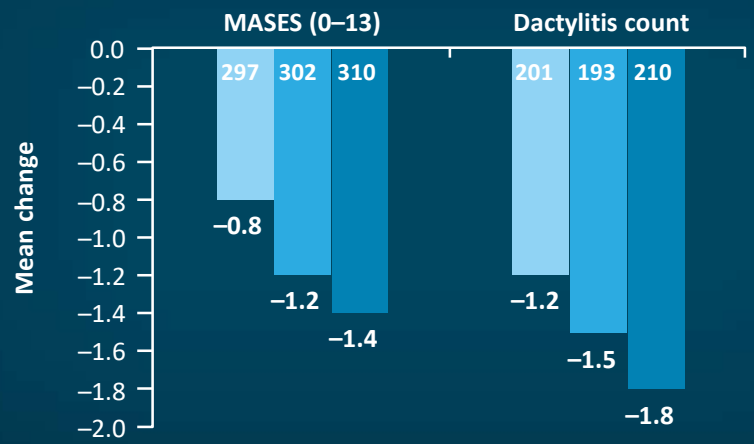
LOCF = last observation carried forward.

Paul C et al. *J Am Acad Dermatol.* 2014;70(5):AB164 (abstract P8412). Papp K et al. *J Am Acad Dermatol.* 2015;73:37-49. Reich K et al. AAD 2013, Late breaker. Paul C et al. *Br J Dermatol.* 2015;173:1387-1399.

45

Apremilast Effects on Enthesitis and Dactylitis

Data pooled from PALACE 1–3, week 24



Gladman DD, et al. *Arthritis Rheum*. 2013;65(10 suppl): S347 (abstract 816).

46

PALACE 2: 52-Week Safety of Apremilast[1]

Adverse Events	Placebo (N = 159)	APR 30 BID (24 weeks) (N = 162)	APR 30 BID (52 weeks) (N = 234)
Diarrhea	8 (5.0)	24 (14.8)	32 (13.7)
Nausea	3 (1.9)	26 (16.0)	32 (13.7)
Headache	7 (4.4)	19 (11.7)	23 (9.8)
URTI	6 (3.8)	11 (6.8)	22 (9.4)
Nasopharyngitis	6 (3.8)	8 (4.9)	10 (4.3)
Hypertension	7 (4.4)	5 (3.1)	13 (5.6)
Laboratory values			
ALT >150 u/L	1/158 (0.6)	2/160 (1.3)	3/230 (1.3)
Creatinine elevation	0/158 (0.0)	1/160 (0.6)	2/230 (0.9)

Warnings for[2]:

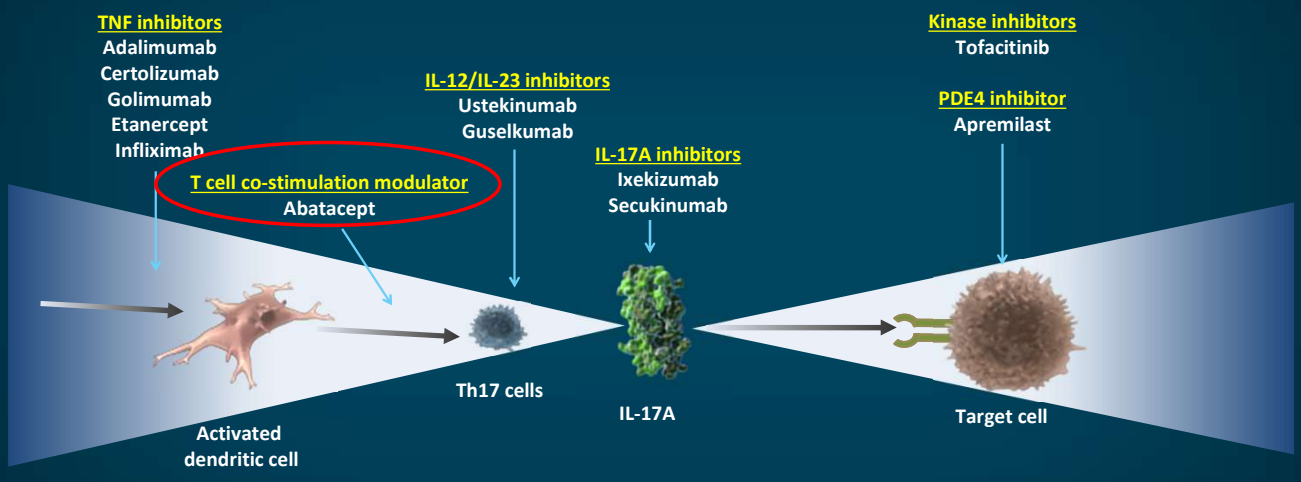
1. Depression and suicidal behavior
2. Weight loss

APR = apremilast; ALT = alanine aminotransferase.

1. Cutolo M, et al. *J Rheumatol.* 2016;43:1724-1734. 2. Apremilast (Otezla ®) PI (http://media.celgene.com/content/uploads/otezla-pi.pdf).

47

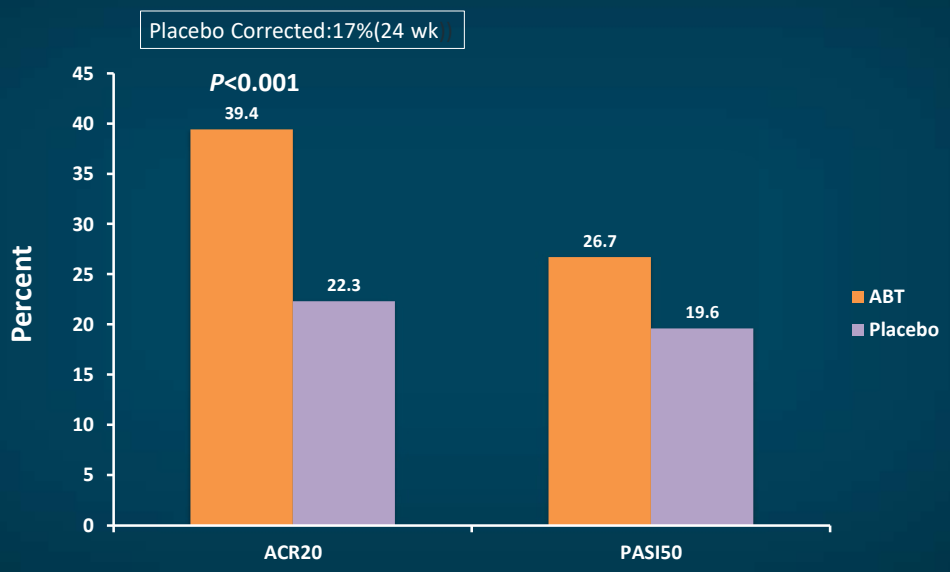
Current and Novel Treatment Options for PsA Treatment



Adapted from Nestle FO et al. *N Engl J Med*. 2009;361:496-509. Kopf M et al. *Nat Rev Drug Discov*. 2010;9:703-718. Garber K. *Nat Biotechnol.* 2011;29:563-566. Thanks to Iain McInnes.

48

Abatacept: Phase III Trial



ABT = abatacept.

Mease PJ, et al. *Ann Rheum Dis*. 2017;76:1550-1558.

49

Summary

- Pharmacologic treatment of PsA is only 1 part of the picture. Other factors to consider include:
- Patient goals
  - Improve quality of life, function, and social participation
  - Control symptoms and inflammation (enthesitis, dactylitis, joint pain)
  - Prevent joint damage
- Starting treatment early
- Minimizing associated comorbidities.
- Multidisciplinary care:
  - Physical therapy, occupational therapy, management of comorbidities by dermatologists, endocrinologists, cardiologists, etc.

Perez-Chada LM, et al. *Clin Immunol*. 2020;108397.

50

Case Study

Inflammatory Bowel Disease

51

Initial Presentation

- 55-year old woman reports worsening pain and stiffness in her fingers, ankle pain, and swelling of her finger and elbow
- Physical exam:
  - Tenderness in right 3 DIPs, bilateral 4 PIPs
  - Dactylitis of right finger
  - Left elbow swollen and tender
  - Right ankle swollen with enthesitis present
  - CDAI: 20
- Plaque psoriasis present on elbows, forearms, trunk and scalp
  - Scaling with minor fissures. PASI:12

52

History of Present Illness

- PMH: hypertension, type 2 diabetes, obesity
- Diagnosed with psoriasis 8 years ago and PsA 1 year ago
- Initially managed with methotrexate (15 mg/week)
  - Elevated AST and ALT two months after starting methotrexate
- Patient switched to cyclosporine A
  - She complained of worsening symptoms with DAS28 of 5.8 and PASI of 11
  - Cyclosporine discontinued
- Patient is currently taking etanercept 50 mg/week

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Lab Results

Lab	Results	Normal Range
Hemoglobin	13 g/dL	12.0-15.5 g/dL
WBC	6800 cells/µL	4500-11,000 cells/µL
ESR	**27 mm/hr**	0-22 mm/hr
RF	9 IU/mL	0-20 IU/mL
CCP	12 u/mL	0-20 u/mL
CRP	**70 mg/L**	<10 mg/L
HbA1c	7.1%	<5.7%

How would you manage this patient?

54

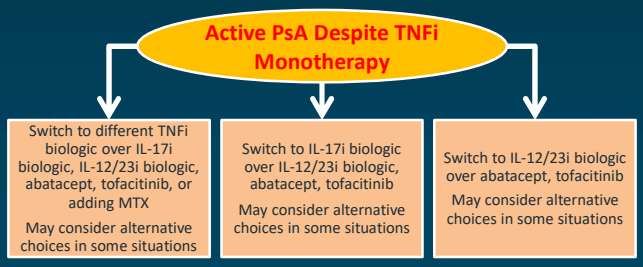
Management

- Patient is switched from etanercept to ixekizumab
  - She reports a significant decrease in tenderness and swelling of fingers and elbow
  - Resolution of dactylitis
  - Psoriatic skin lesions disappeared
  - CRP falls from 70 to 15 mg/L
- 6 months later, the patient complains of abdominal pain and frequent episodes of diarrhea
  - The patient is referred to a gastroenterologist and is diagnosed with Crohn's disease

How would you manage this patient?

55

Conclusions



- Crohn's disease and ulcerative colitis, including exacerbations, occurred during clinical trials of IL-17 inhibitors. Monitor for inflammatory bowel disease with secukinumab or ixekizumab. Initiate appropriate medical management if IBD develops.
- FDA-approved medications for IBD include:
  - Crohn's disease: adalimumab, infliximab, ustekinumab, and certolizumab pegol
  - Ulcerative colitis: adalimumab, infliximab, ustekinumab, and golimumab

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Case Study

COVID-19 Vaccination

57

COVID-19 Vaccination

- 39-year old man was first diagnosed with psoriasis 8 years ago and was managed with topical therapy and phototherapy
- He began to experience polyarthritis 1 year ago and was prescribed methotrexate
  - His symptoms are well-controlled with MTX
- The patient is an essential worker and has signed up for the COVID-19 vaccine

How would you manage this patient's treatment regimen given his upcoming vaccination?

58

Follow-up Appointment

- The patient arrives at a follow-up appointment 6 months later with an increasing number of psoriatic plaques and pain and stiffness in his fingers, wrist and lower back
  - CDAI: 28, pain: 4, global: 6
  - 4 left (L) distal interphalangeal (DIP) joints tender
  - 4 right (R) DIP joints tender
  - 4 L, R proximal interphalangeal (PIP) joints tender
  - L wrist swollen and tender
  - No enthesitis

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Lab Results

Lab	Results	Normal Range
Hemoglobin	14 g/dL	12.0-15.5 g/dL
WBC	7200 cells/µL	4500-11,000 cells/µL
ESR	**35 mm/hr**	0-22 mm/hr
CRP	9 mg/L	<10 mg/L
CCP	10 u/mL	0-20 u/mL
AST	20 u/L	10-40 u/L
ALT	41	7-56 u/L

How would you manage this patient?

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Response to Therapy

- The patient is prescribed etanercept
  - His CDAI fell from 28 to 10
  - He reports improvement in his scalp psoriasis
  - He returns to work 1 month after initiating therapy

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Thank You for Your Attention!

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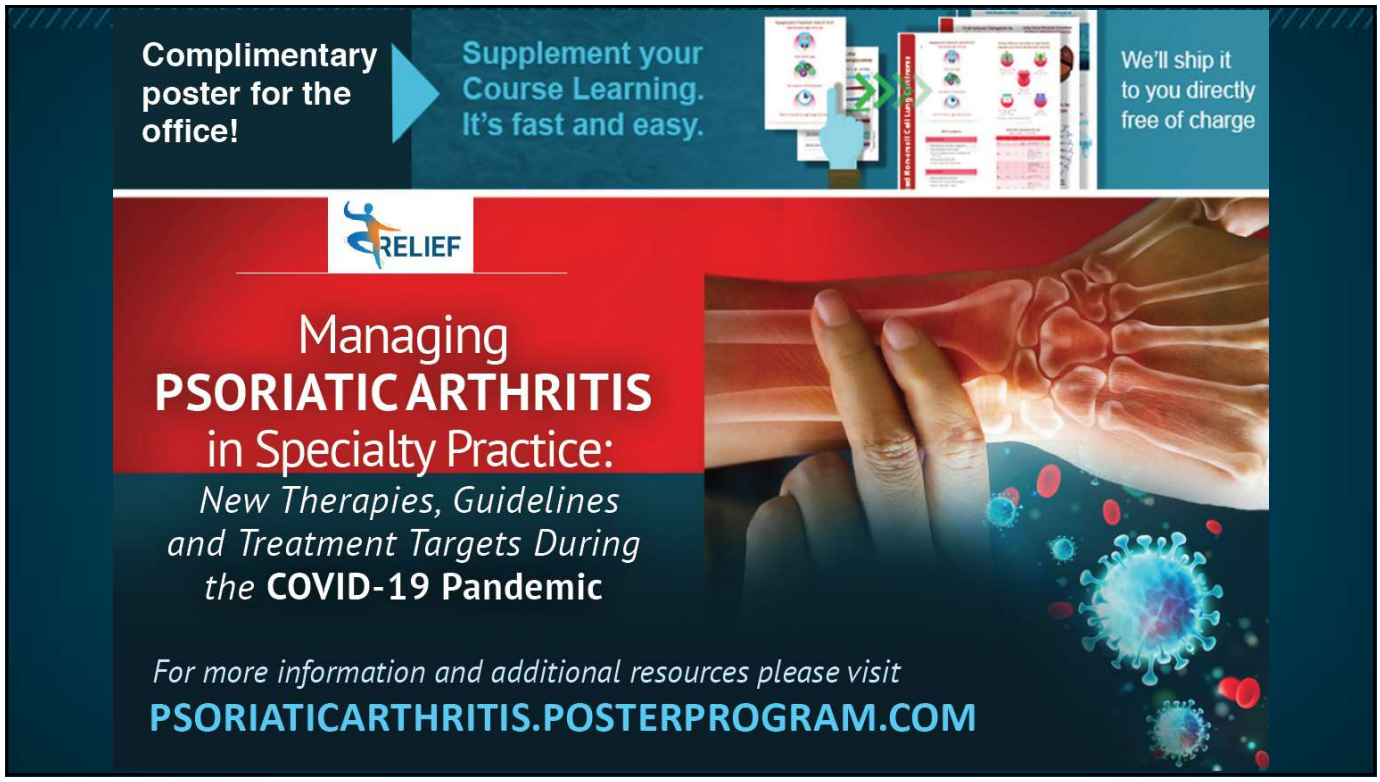
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