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RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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VIRTUAL CONFERENCE

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Psoriatic Arthritis:
Scratching the Surface

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Disclosure

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Faculty Disclosures

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There are no disclosures at this time.

Objectives

- PsA Clinical Features/Domains
- Comorbidities Common in PsA
- Patient Specific Therapeutic Options

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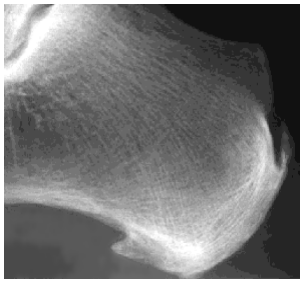
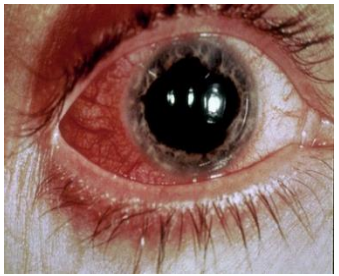
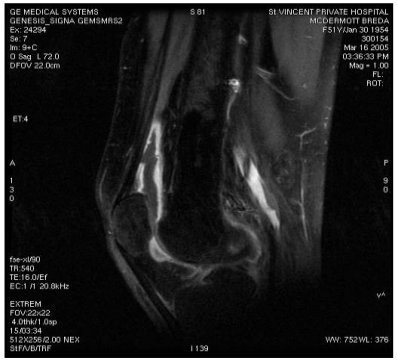
Part 1: Psoriatic Arthritis Clinical Features

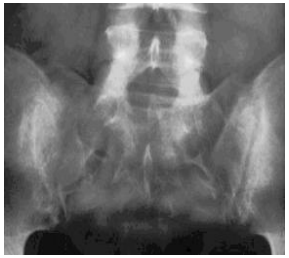
Psoriatic Disease

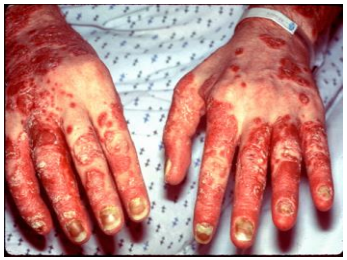
Complex, polygenic autoinflammatory disease with diverse clinical features

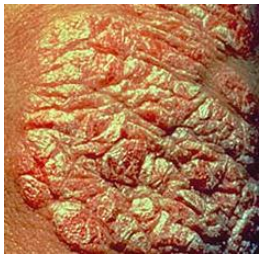


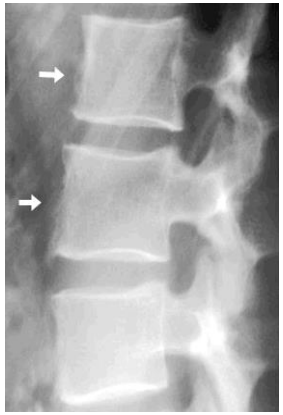


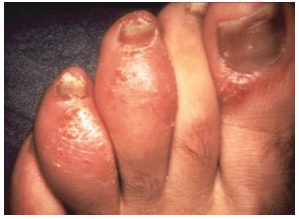


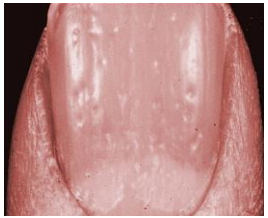


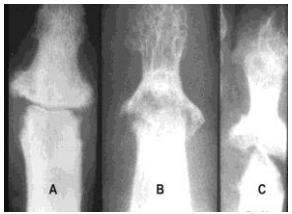












Slide courtesy of Dr. Philip Mease

Clues to Pathogenesis

- 40% have a positive family history
- HLA-B27 positive 15-50%, greater in PsA spondylitis (60%)
- Male/Female ratio ~1:1
- Age onset 30-50
- Environmental triggers:
  - trauma (Koebner phenomena)
  - Infection
  - Stress
  - Obesity
- **In 60-70% of cases, psoriasis precedes joint disease**

Five Disease Domains

1. **Skin and nails**: ~90% have skin involvement.[1] 87% have nail changes.[5]
2. **Arthritis**: Characteristic joint space narrowing and erosions[(2,3)]
3. **Dactylitis**: 32-48%[4] of patients
4. **Enthesitis**: 25-53%[4] of patients
5. **Spondylitis**: ~20-40% of patients with peripheral joint disease have axial involvement[6]

1. Peluso R, Iervolino S, Vitiello M, Bruner V, Lupoli G, Di Minno MND. Extra-articular manifestations in psoriatic arthritis patients. *Clin Rheumatol*. 2015;34:745-753.
2. Gottlieb A, Korman NJ, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol*. 2008;58:851-864.
3 Sudoł-Szopińska I, Matuszewska G, Kwiatkowska B, Pracoń G. Diagnostic imaging of psoriatic arthritis. Part I: etiopathogenesis, classifications and radiographic features. *J Ultrason*. 2016;16:65-77.
4. Liu J-T, Yeh H-M, Liu S-Y, Chen K-T. Psoriatic arthritis: epidemiology, diagnosis, and treatment. *World J Orthop*. 2014;5:537-543.
5. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis.* 2005;64(suppl 2):ii14-ii17. doi:10.1136/ard.2004.032482.
6. Lubrano E,Marchesoni A. Olivieri I, D'Angelo S, Palazzi C, Scarpa R, Ferra N, Parsons WJ, Brunese L, Helliwell PS, Spadaro A. The radiologic assessment of axial involvement in psoriatic arthritis, J Rheumatol Supp, 2012;89:54-6

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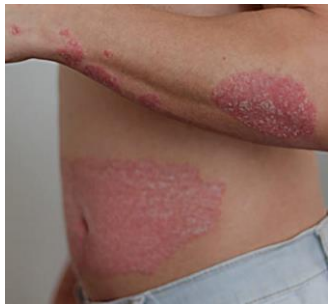
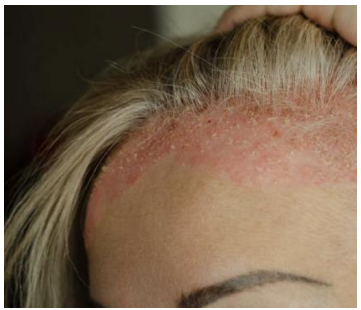
1. Skin and Nails

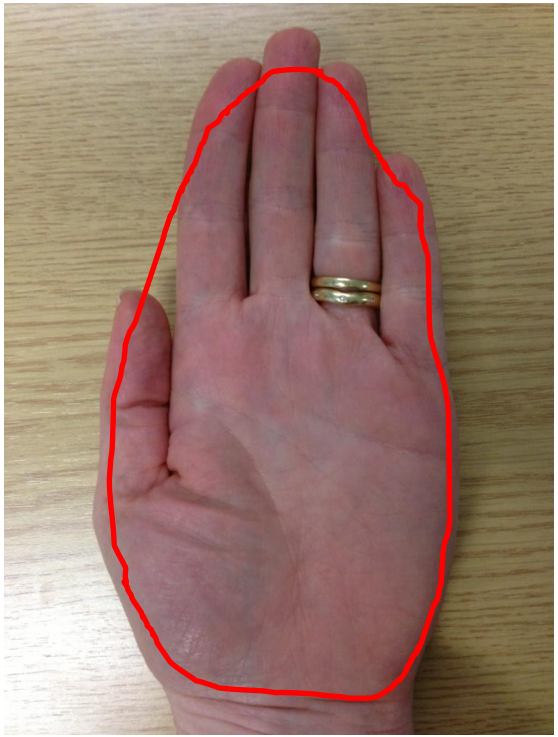
Body Surface Area (BSA)

Body surface area commonly used

- 1% BSA = 1 handprint
  - PATIENT's hand! (**includes thumb**)
- Head and Neck = 10% (10 handprints)
- Upper extremities = 20%
- Trunk (axillae and groin) = 30%
- Lower extremities (buttocks) = 40%







What is a **PASI** and why is it important?

Psoriasis Area and Severity Index (PASI):

- Score from 0-72
- Includes:
  1. **Plaque qualities** (erythema, thickness, scaling scored 0-4 over 4 different body areas)
  2. **Area of body** (scored 0-6 based on percentage of coverage for each of 4 body areas)
- Used as an outcome measure in clinical trials
- Detects change
- There's an app for that!

Naldi et. Randomized Clinical Trials for Psoriasis 1977–2000: The EDEN Survey, JID 2003

Induration:

Elevation of the skin lesion relative to the normal surrounding skin

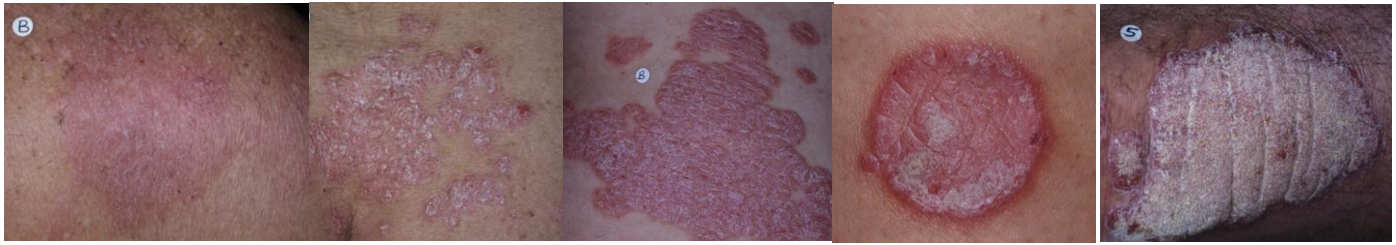
0 = none

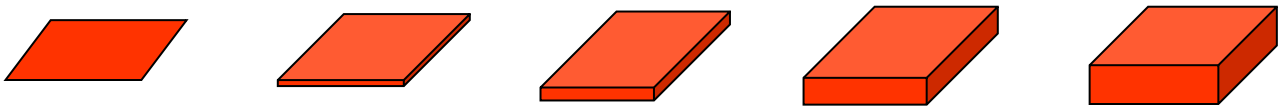
1 = slight (but definite to touch)

2 = moderate (easily palpable with rounded or sloped edges)

3 = severe (elevated with hard sharp borders)

4 = very severe (very elevated with very hard sharp borders)

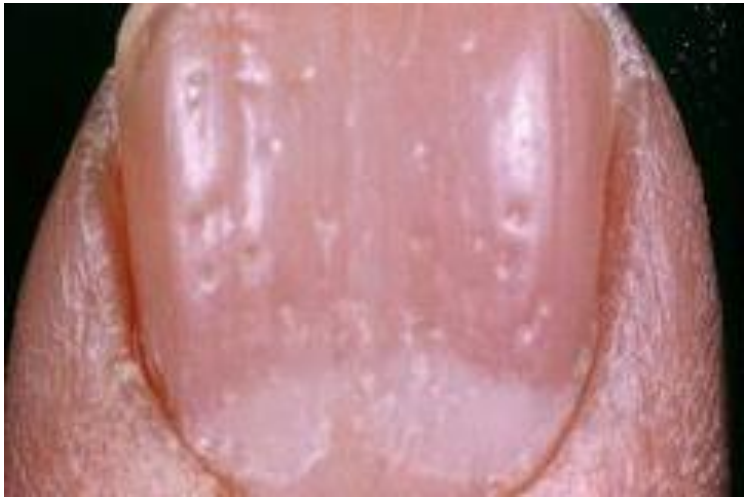


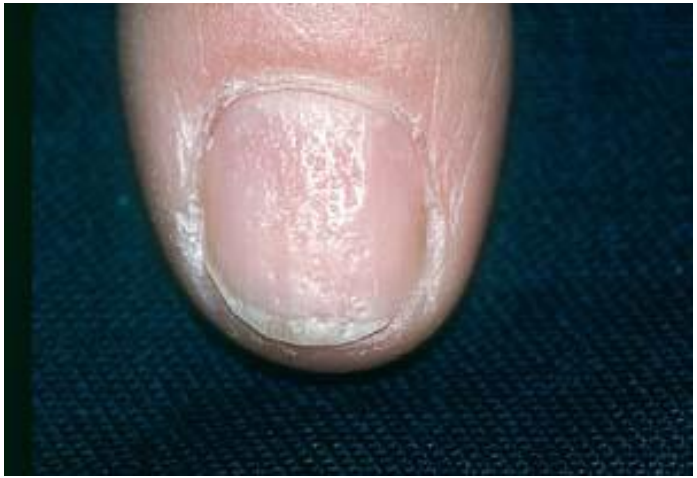


Nails

- **Features of the nail matrix**
  - Pitting
  - Leukonychia
  - Nail plate crumbling
- **Features of the nail bed**
  - Oil drop (salmon patch) discoloration
  - Onycholysis
  - Nail bed hyperkeratosis
  - Splinter hemorrhages

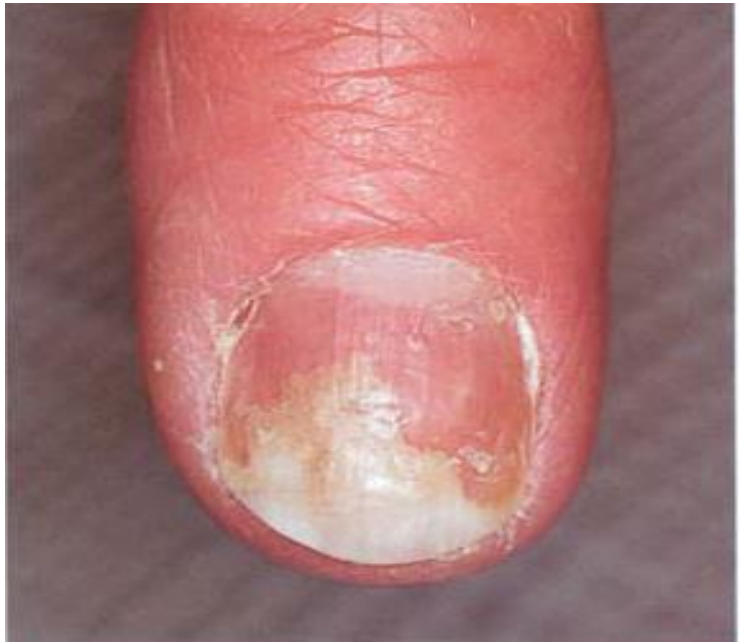
Nail Matrix: Pitting



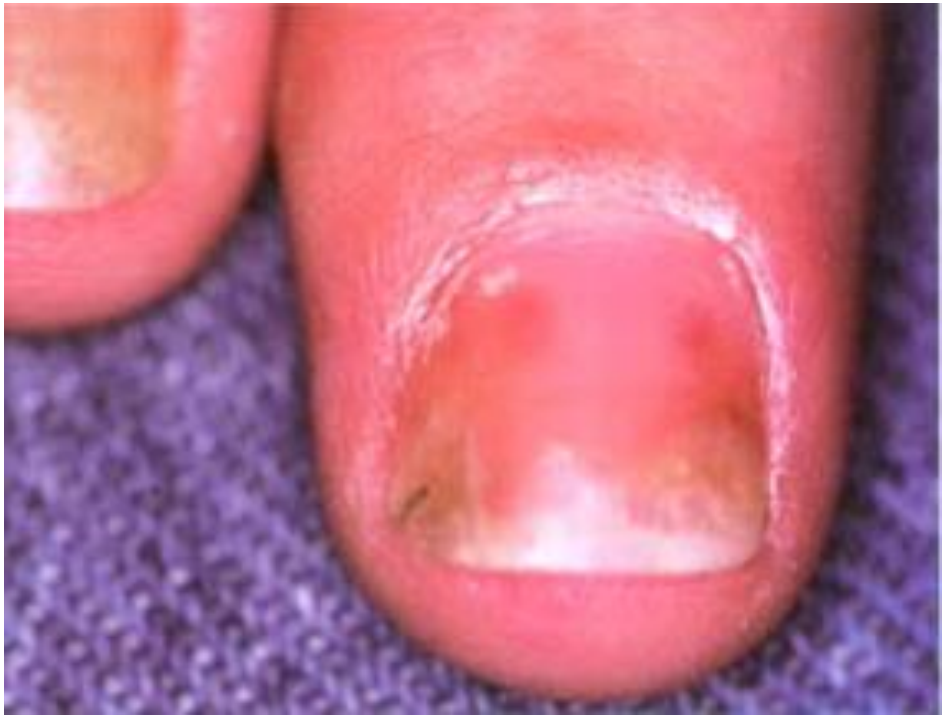


Nail Matrix: Nail plate crumbling

Nail bed: Onycholysis



Nail Bed: Oil drop (salmon patch) discoloration



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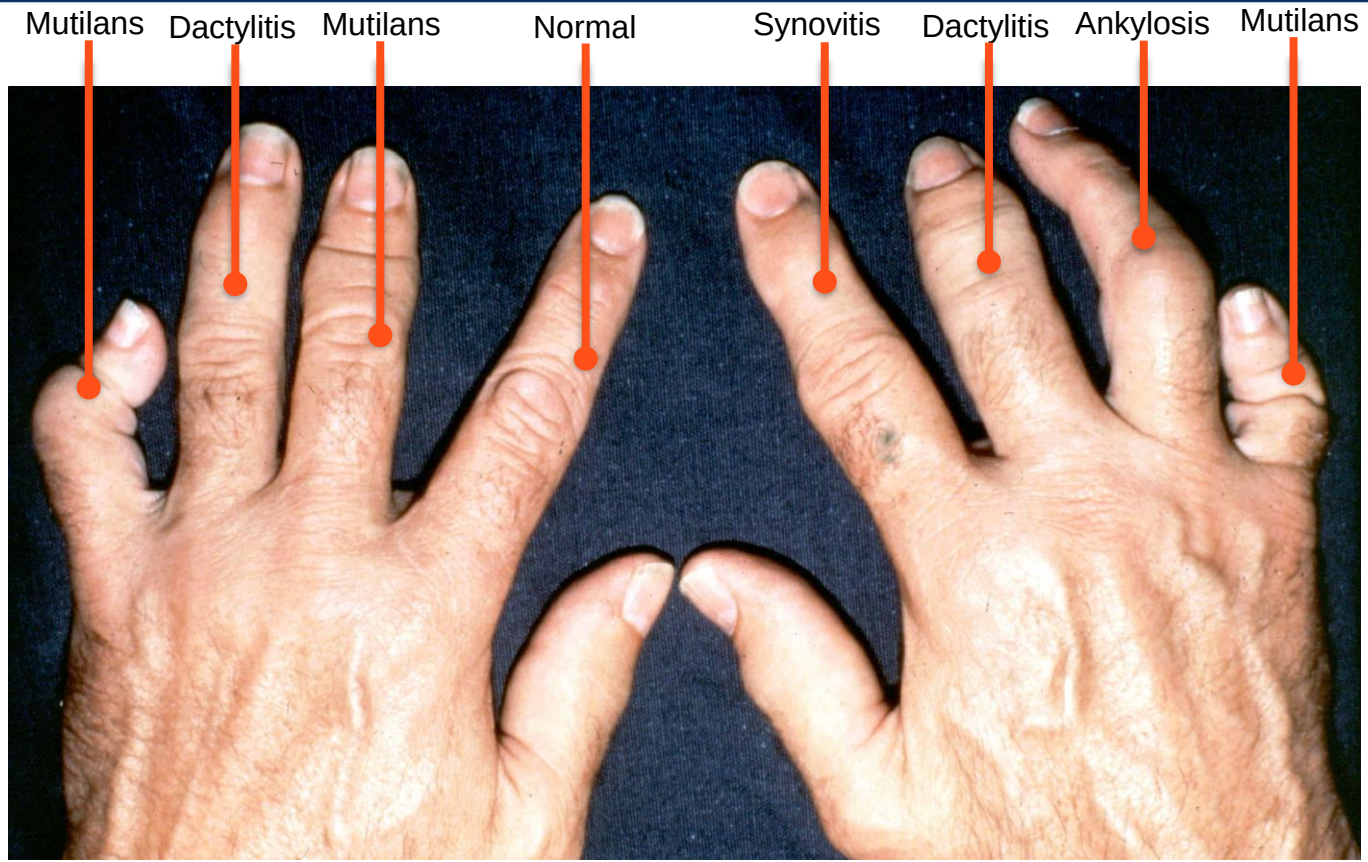
2. Arthritis

Arthritis

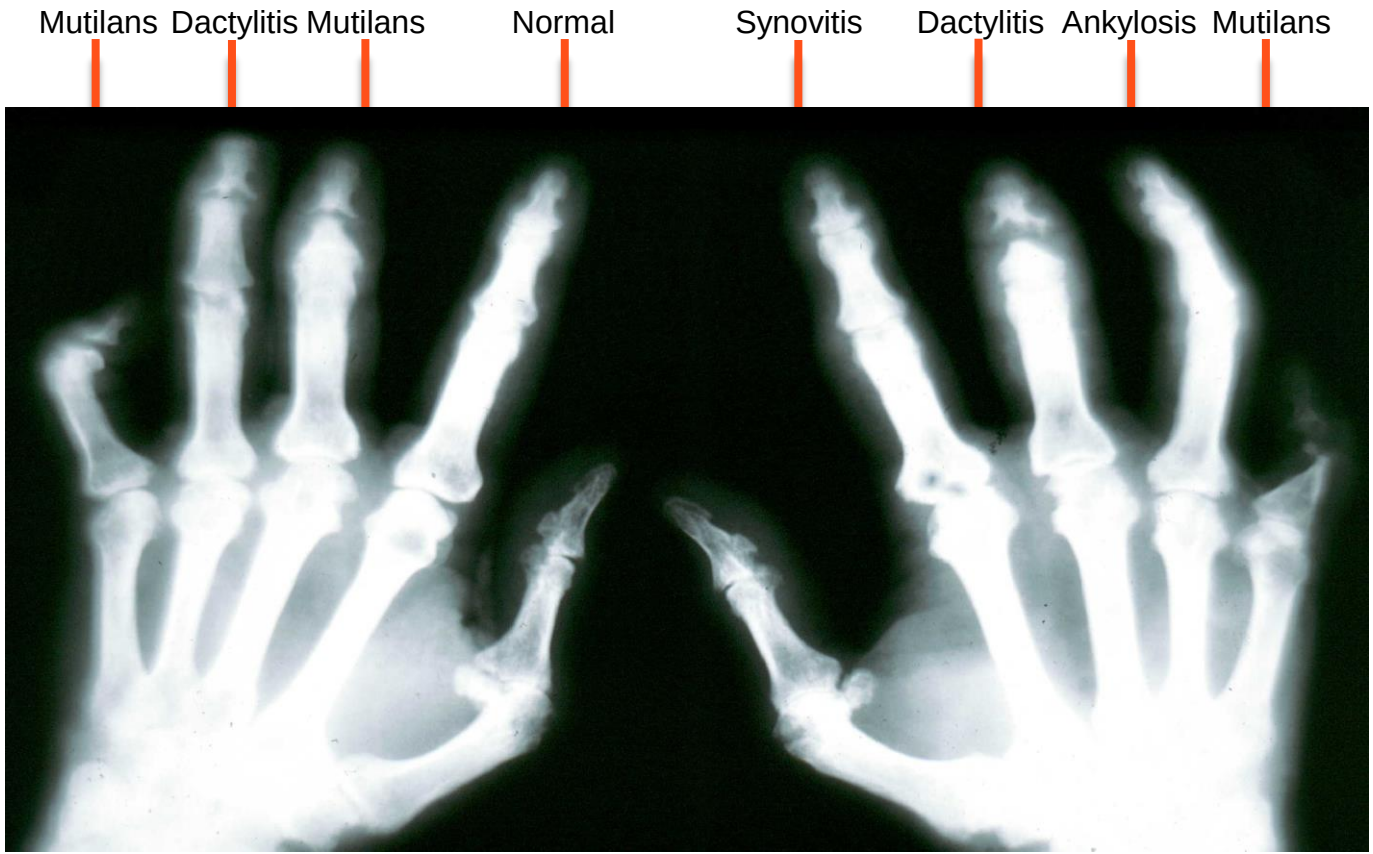
- Most frequently presents as polyarthritis
- Asymmetric OR symmetric
- Distal arthritis, ie. DIP joints
- Arthritis mutilans (pencil and cup deformity)
- Radiographic changes can include:
  - Erosions, new bone formation, periostitis, lysis of terminal phalanges, ankylosis
  - *Many of these can occur in the same digit*

Siannis F, Farewell VT, Cook RJ, jSchentag CT, Gladman DD. Clinical and radiographic damage in PsA. Ann Rheum Dis 2006;65(4):478.

Ray Diversity in PsA

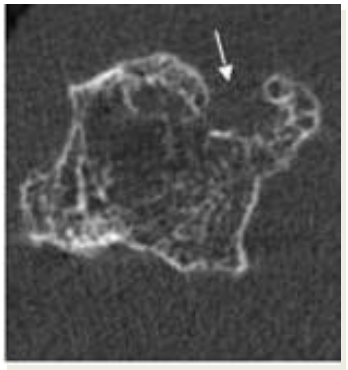


Assessing Structural Damage in PsA – Digit Diversity

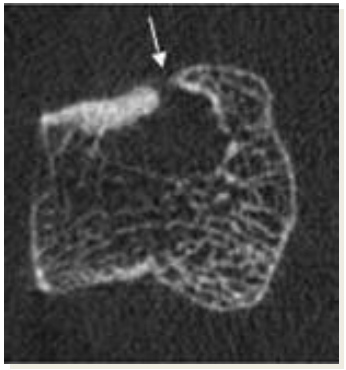


Morphology of erosions in RA and PsA

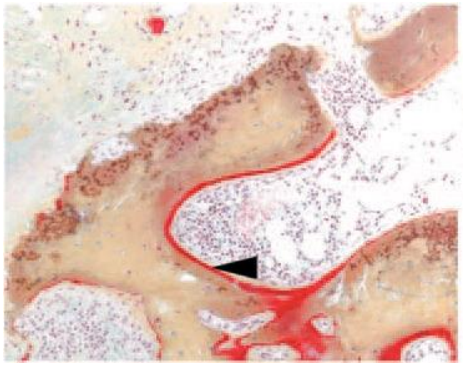
RA



PsA

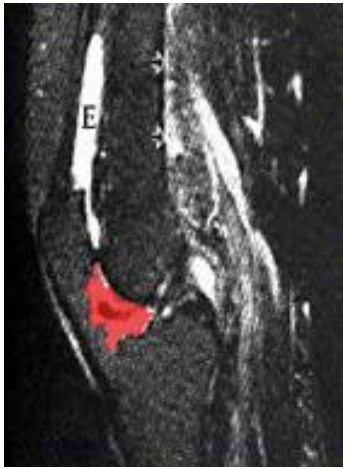


Osteoid Deposition

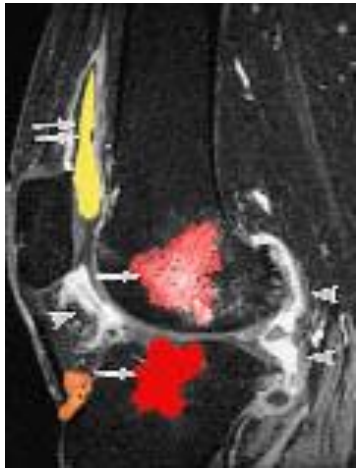


Finzel S et al Ann Rheum dis. Jan 2011;70:122
Jimenez-Bos et al. JI, 2005;175

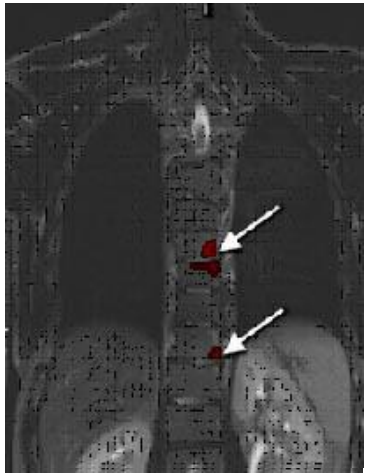
Sites of Joint Inflammation



RA-synovium



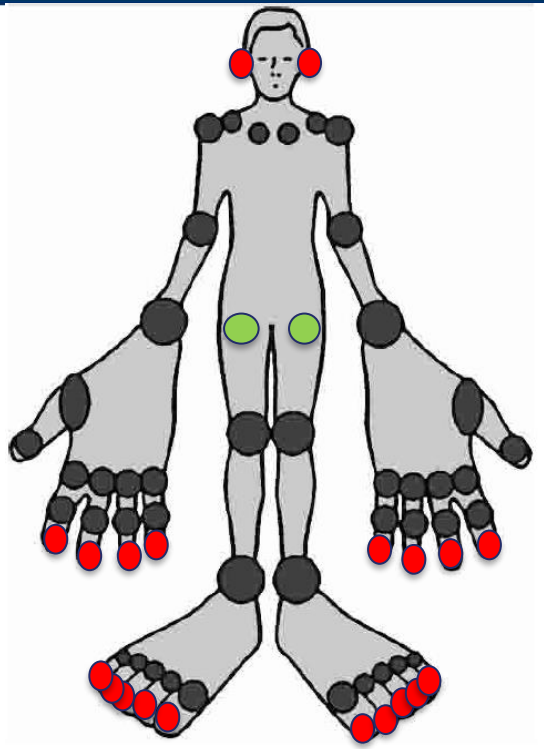
PsA-bone, enthesis and synovium



AS-bone, enthesis

Joint Counts

- Joint Counts
  - **68/66 in PsA**
  - 46/44 in AS
  - 28 in RA



Sieper J. Ann Rheum Dis 2009;68(Suppl II):ii1–ii44. doi:10.1136/ard.2008.104018
Chandran V, et al. Arthritis Rheum 2009;61:1235-42

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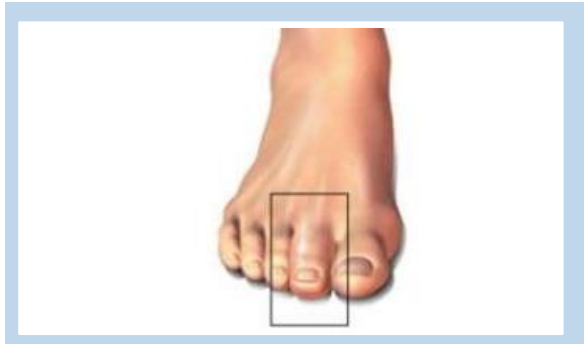
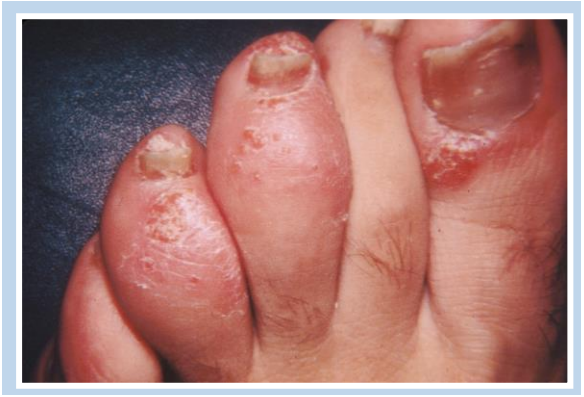
3. Dactylitis

Dactylitis in PsA

- **Dactylitis:** Diffuse swelling of a digit, also referred to as “sausage digit”[1]
- One of the *cardinal features of PsA*, occurring in up to **40% of patients**[1,2]
- Feet commonly affected[1]
- <u>Associated with increased radiologic damage</u>[1]

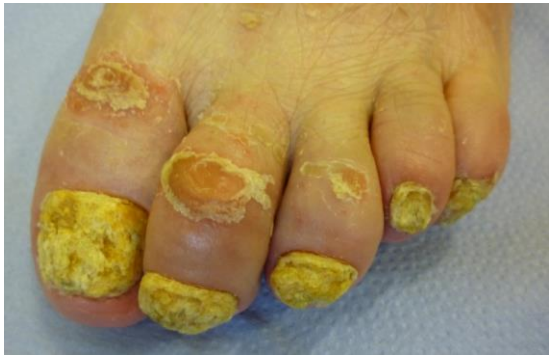


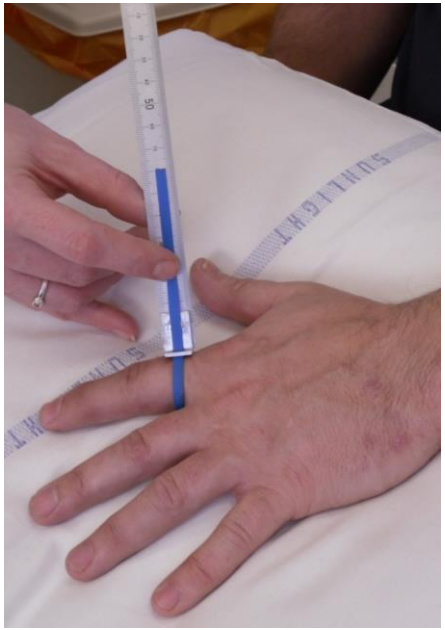


1. Brockbank J, Stein M, Schentag CT, Gladman DD. Dactylitis in psoriatic arthritis: a marker for disease severity? Ann Rheum Dis. 2005;64:188-90.
2. Veale D, Roger S, Fitzgerald O. Classification of clinical subsets in psoriatic arthritis. Br J Rheumatol. 1994;33:133-8.

Dactylitis

- Leeds Dactylitis Index (LDI)
- Count
- Score (0-3)





Leeds Dactylometer

Mease P. Arth Care & Research. 2011;63:64-85

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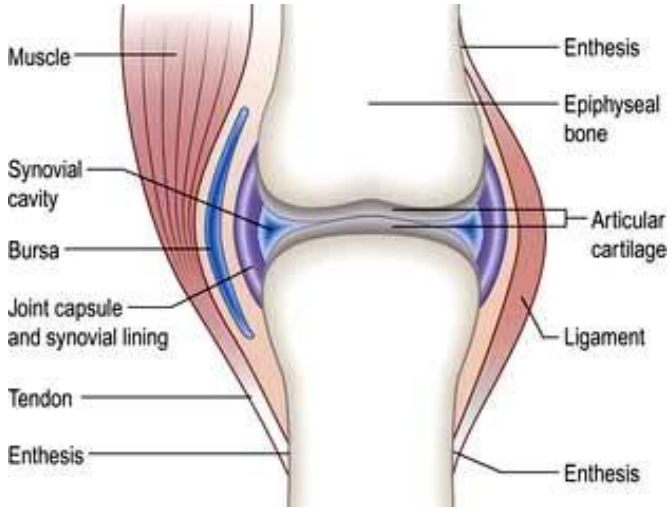
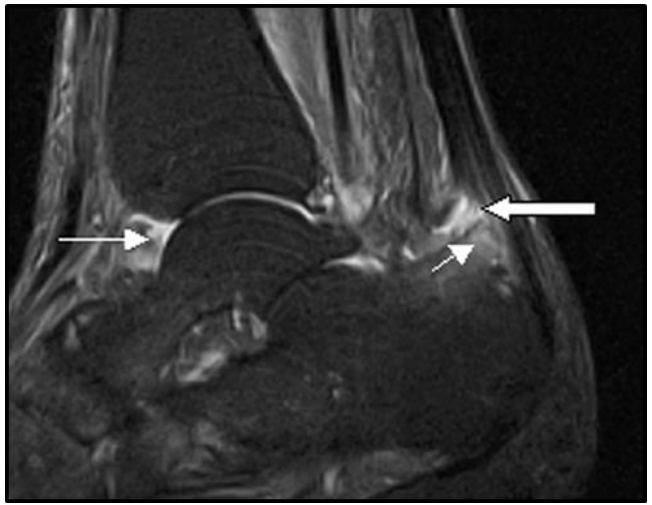
4. Enthesitis

Enthesitis

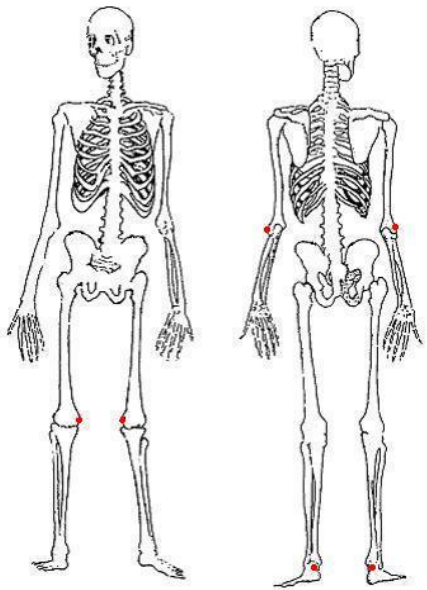
"**Enthesis**" from the Greek word, "ἔνθεσις" or "énthesis," meaning insertion. *The site of attachment of tendons, ligaments or joint capsule fibers to bone*.

Enthesitis is inflammation of the enthesis.

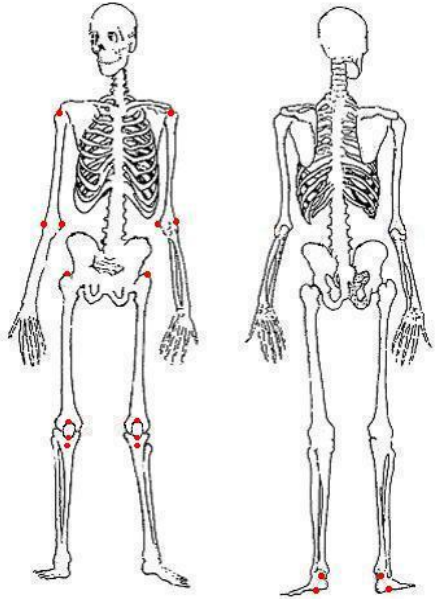




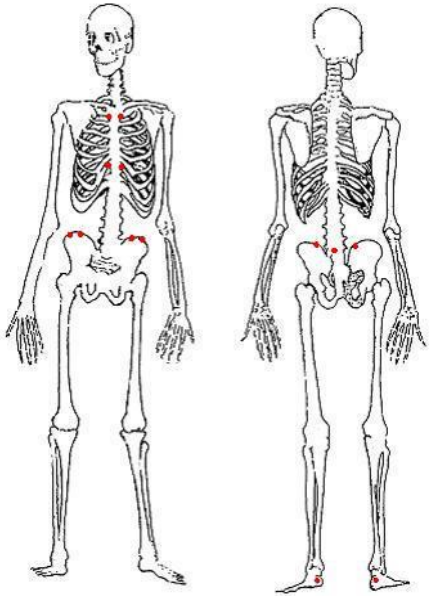
Enthesitis Indices



LEI
6 sites



SPARCC
18 sites; score of 16



MASES
13 sites

Mease P. *Arthritis Care Res* 2011;63:64–85.

Enthesitis: Onset and Prevalence

- In registry studies, up to ***35%*** *of PsA patients present* with enthesitis[13]
- In clinical trials, ***56–79****% of PsA subjects present* with enthesitis[7–12]
- Primary lesion that precedes the diverse skeletal manifestation of PsA in subjects with psoriasis[1,2]
- Isolated peripheral enthesitis **may be the only rheumatologic sign of PsA**
- Subclinical enthesitis is common in patients with PsO and may predict development of PsA[3,4]

1. Simon et al., Ann Rheum Dis Ann Rheum Dis. 2016;75:660-6, 2. Takata T, et al. *J Dermatol.* 2016;43:650–4; 3. Ozçakar L, et al. *Int J Dermatol*. 2005;44:930-2; 4. Tinazzi I et al. *J Rheumatol*. 2011;38:2691–2; 5. McGonagle D, et al. *Ann Rheum Dis*. 2002;61:534–7; 6. Benjamin M, et al. *Arthritis Rheum.* 2007;56:224–33; 7. Mease P, et al. *N Engl J Med*. 2015;373:1329-39; 8. McInnes IB, et al. *Lancet*. 2015;386:1137-46; 9. McInnes IB, et al *Lancet*. 2013;382:780-9; 10. Kavanaugh A, et al. *Arthritis Rheum*. 2009;60:976-86; 11. Mease P, et al. *Ann Rheum Dis*. 2014;73:48-55; 12. Kavanaugh A, et al. *Ann Rheum Dis*. 2014;73:1020-6; 13. Polachek A, et al. Arthritis Care Res (Hoboken). 2016 Dec 20

Enthesitis and Dactylitis as Markers of Greater Disease Activity and Negative Patient Impact

- Corrona PsA-SpA registry (N=1567)

- Presence of dactylitis and enthesitis correlated with:
  - Worse measures of disease activity (eg.CDAI, CRP)
  - Worse function (HAQ)
  - Worse pain, fatigue, work productivity
  - Less likely to achieve Minimal Disease Activity (MDA) state

Mease P, et al. Arthr Care Res. 2017. 69: 1692-1699

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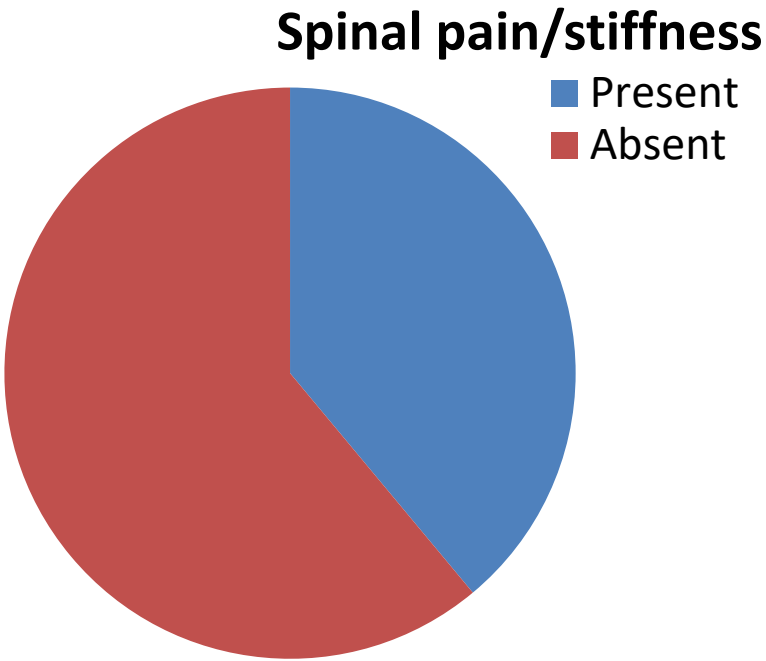
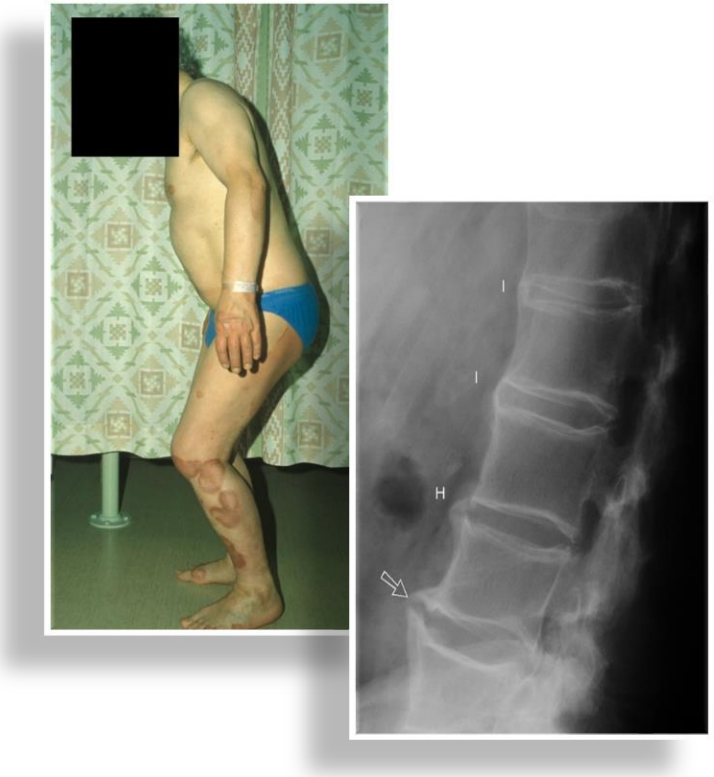
5. Spondylitis

Spine Disease





Helliwell, et al. *ARD*. 2007;66:113-7.
Coates, et al. J Rheum. 2011 Jul;38(7):1496-501
Mease P. Arth Care & Research. 2011;63:64-85

Axial involvement in Psoriatic Arthritis

- Asymmetric sacroiliitis[1]
- Nonmarginal and asymmetrical syndesmophytes[1]
- Paravertebral ossification[1]
- Frequent involvement of cervical spine[1]
- Spondylitis without sacroiliitis more common in PsA than in AS
- HLA-B27, Nail dystrophy, number of radiographically damaged joints, periostitis and elevated ESR increased the risk of developing AxPsA, whereas swollen joints decreased risk [2]

1. Lubrano E,Marchesoni A. Olivieri I, D'Angelo S, Palazzi C, Scarpa R, Ferra N, Parsons WJ, Brunese L, Helliwell PS, Spadaro A. The radiologic assessment of axial involvement in psoriatic arthritis, J Rheumatol Supp, 2012;89:54-6
E2. Chandran V, et al. J Rheumatol 2010; 37:809-5

PsA with axial involvement vs AS

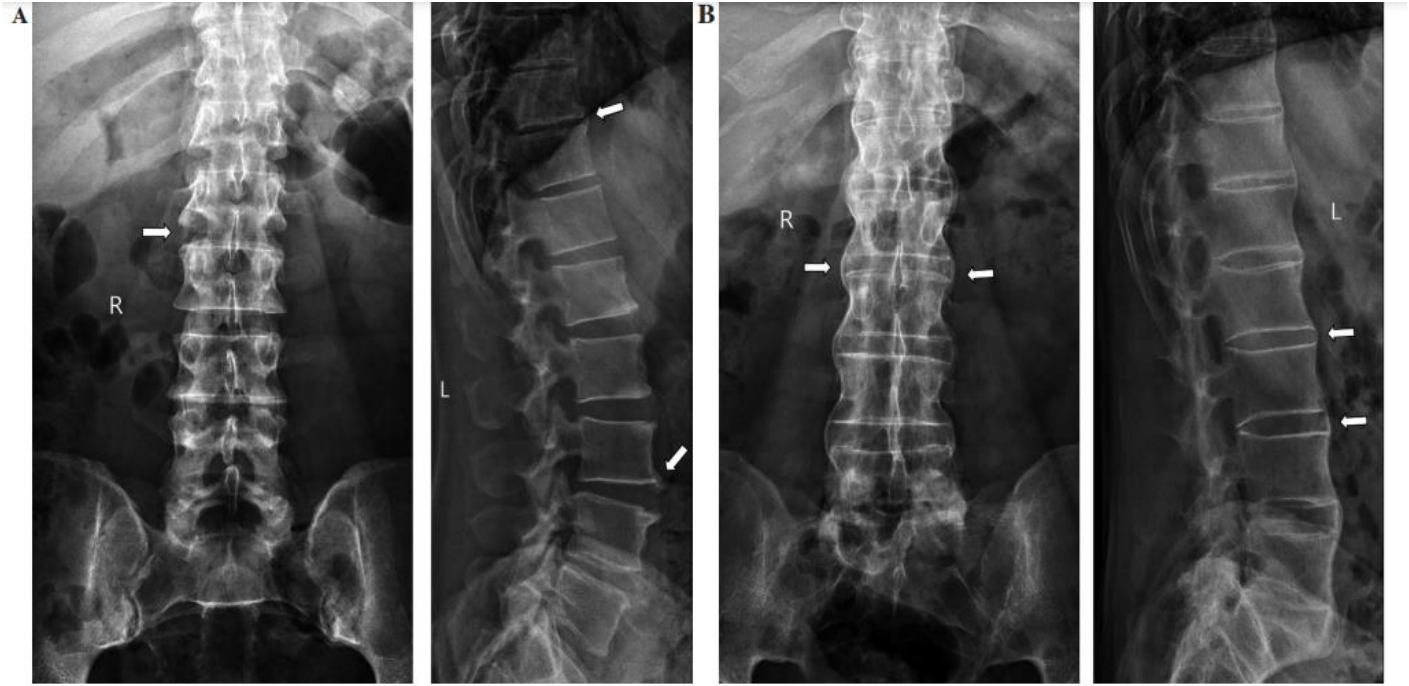


Fig. 1. Example of conventional radiographs of the lumbar spine from a patient with psoriatic arthritis with axial involvement (PsA, Fig. A) and ankylosing spondylitis (AS, Fig. B) Overall, radiographic evidence of syndesmophytes is less common in PsA than in AS. Spinal disease in PsA is more frequently unilateral, the syndesmophytes show a larger volume, do not follow exactly the course of the anterior longitudinal ligament and do not appear in consecutive vertebrae, as compared to AS.

Baraliakos X, Coates L, Braun J.,Clin Exp Rheumatol 2015; 33 (Suppl. 93): S31-S35

Classification criteria for PsA (CASPAR)

Established inflammatory musculoskeletal disease (joint, spine, or entheseal) With 3 or more of the following		
1. Psoriasis	(a) Current*	Psoriatic skin or scalp disease present today as judged by a qualified health professional
	(b) History	A history of psoriasis that may be obtained from patient, or qualified health professional
	(c) Family history	A history of psoriasis in a first or second degree relative according to patient report
2. Nail changes		Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination
3. A negative test for RF		By any method except latex but preferably by ELISA or nephlometry, according to the local laboratory reference range
4. Dactylitis	(a) Current	Swelling of an entire digit
	(b) History	A history of dactylitis recorded by a qualified health professional
5. Radiological evidence of juxta-articular new bone formation		Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain xrays of hand or foot

Current psoriasis awarded 2 points

Criteria specificity 98.7%, sensitivity 91.4%

Taylor WJ, et al. Arth Rheum 54: 2665-2673, 2006

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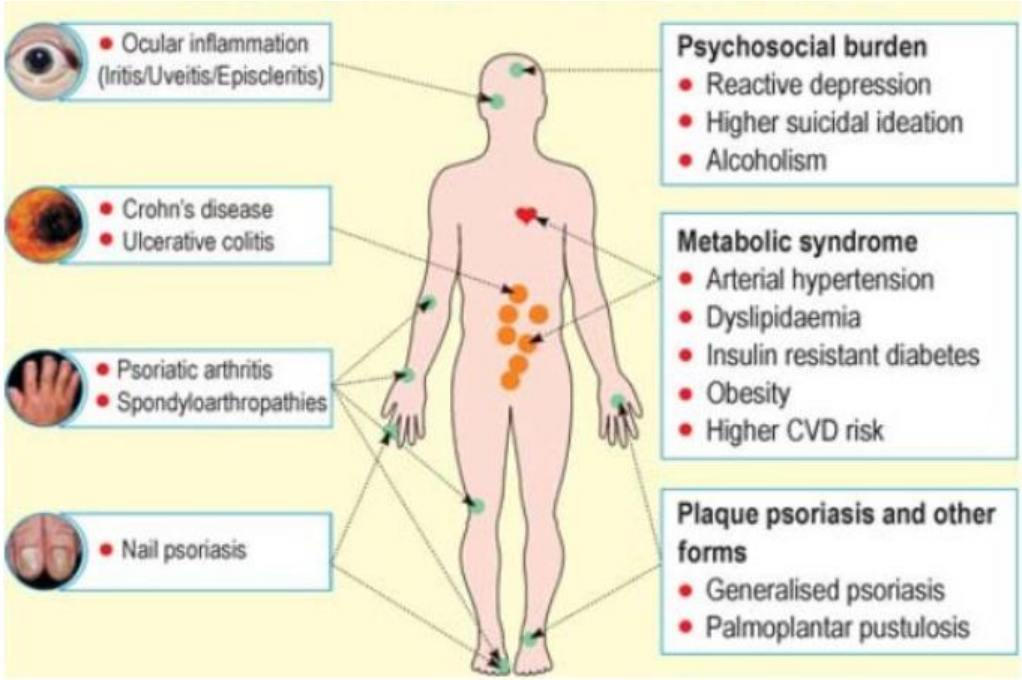
Part 2: Comorbidities

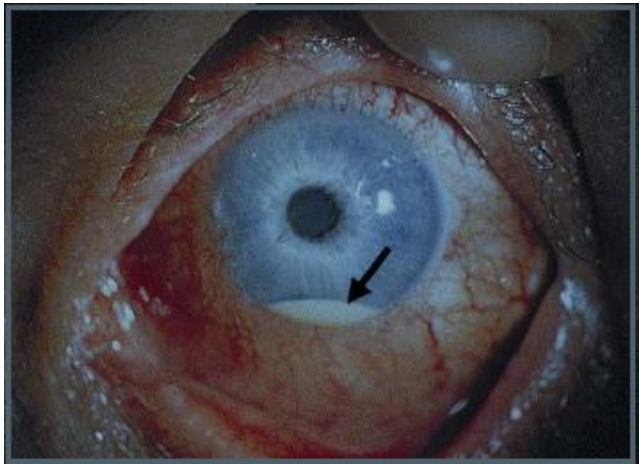
Comorbidities to consider in PSA



Aurangabadkar SJ. Comorbidities in psoriasis. Indian J Dermatol Venereol Leprol [serial online] 2013 [cited 2020 Nov 23];79, Suppl S1:10-7. Available from: https://www.ijdvl.com/text.asp?2013/79/7/10/115506

Uveitis

- Uveitis is observed in **9-25% of PsA patients** (15-20% of PsO patients)
- Bilateral in 37.5% of patients
  - vs only 7% b/l in SpA patients
- 44% posterior in PsA patients
  - vs 17% posterior in SpA patients



22.7% HLA-B27 positive

Associated with dactylitis

Paiva ES *et al*. *Ann Rheum Dis* 2000; 59:670
Niccoli L et al., Int J of Rheum Dis 2012; 15:414-418

Inflammatory bowel disease (IBD)

Patients with psoriatic arthritis had a **2.74-fold risk of developing CD** and a **1.74-fold risk of developing UC** when compared with controls.

(Yu Ru, Chen-Han Lee, Ching-Chi Chi. **Association of Psoriasis With Inflammatory Bowel Disease:** A Systematic Review and Meta-analysis JAMA Dermatol. 2018 Dec; 154)(12): 1417–1423

Cardiovascular Risk Factors

- HTN found in 30% of PsA patients [1,2]
- Dyslipidemia ↑ Triglycerides and ↓ HDL
  - worse in active disease [3,4]

- Higher prevalence of *dyslipidemia, HTN, and metabolic syndrome in PsA* when compared to RA or AS [5]
- PsA patients have an **increased risk of early MIs**[6]

1.Han C, Robinson DW Jr, J Rheumatol 2006;33:2167–72. 2.Zisman D, Eder L, Rheumatol Int 2012;32:595–600. 3.Tam LS, Tomlinson B, Rheumatology(Oxford) 2008;47:718–23.
4.Jones SM, Harris CP, Ann Rheum Dis 2000;59:904–9. 5.Mok CC, Ko GT, Arthritis Care Res (Hoboken). 2011;63:195–202 6. Gelfand J. JAMA 2006

Obesity

- 81% of PsA patients are overweight or obese
- The presence of obesity was associated with:
  - Higher level of **pain**
  - Greater **skin** involvement
  - Worse **functional capacity** [1]
- Diabetes, obesity, and metabolic syndrome more prevalent in PsA than controls [2,3]
- Potential increase for “fatty liver disease”
- **Liver abnormalities** are common in patients with PsA and are associated with:
  - Higher BMI
  - More **severe disease**[4]

1. Zaffarana C, Gallino Yanzi J, Cerda OL, Landi M, Schneeberger E, Citera G. Prevalence of Obesity in Patients with Psoriatic Arthritis and Its Impact on the Severity of the Disease [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10).
2.Tam LS, Tomlinson B, Rheumatology(Oxford) 2008;47:718–23.
3.Zisman D, Eder L, Rheumatol Int 2012;32:595–600.
4. Pakchotanon rattapol, Liver abnormalities in patients with PsA Journal of Rheum June 2020, 47

Obesity & Moderate Disease Activity (MDA) prediction: a prospective PsA study

- Active PsA patients starting TNFi therapy
- At 12 months, 98/270 achieved MDA
  - Prevalence of obesity lower in group achieving MDA (25% vs. 64% P<0.001)

BMI (kg/m^2)	HR (95% CI) (vs non-obese)	P value
30-35	3.98 (1.96–8.06)	<0.001
> 35	5.40 (3.09–9.43)	<0.001

= Obesity may interfere with response to TNFi therapy in PsA

Di Minno M, et al. Arthritis Care & Res. 2013 Jan;65(1):141-7

Weight loss & MDA in PsA on TNFi

- 138 obese PsA pts starting TNFi
  - Randomized to hypocaloric diet (intervention group) vs. self-managed diet (control group)
- At 6-mo, >10% weight loss associated with greater likelihood of MDA (P=0.001)
- Dose response for MDA based on BMIΔ:
  - HR= 2.05 for 5-10% BMIΔ
  - HR=4.79 for >10% BMIΔ

= Weight loss improves response to TNFi

Di Minno et al., Ann Rheum Dis 2012; Coates LC et al Arthritis Rheumatol. 2016 May;68(5):1060-71

Depression

- In patients with psoriasis, psychiatric disorders can both result from and contribute to disease progression, suggesting overlapping biological mechanisms
- Prevalence study of 520,000 PsA patient found that **39% considered PsA a large problem in their everyday lives**
- Wu et al. found the risk of depression in patients was 14 and 22% higher in patients with psoriasis and PsA when compared to the general population
- In a study comparing RA and PsA pts, **PsA patients had significantly worse QoL compared with RA**: skin involvement may be important
- PsA patients with comorbid depression have poorer response to therapy and adherence to treatment is often more difficult

Gelfand et al JAAD 2005
Husted et al AR 2001
Ferreira BI, Abreu JL, Reis JP, Figueiredo AM. Psoriasis and associated psychiatric disorders: a systematic review on etiopathogenesis and clinical correlation. J Clin Aesthet Dermatol. 2016;9:36–43
Mathew A., Chandran V., Depression in PsA Rheumatol Ther (2020) 7:287–300.

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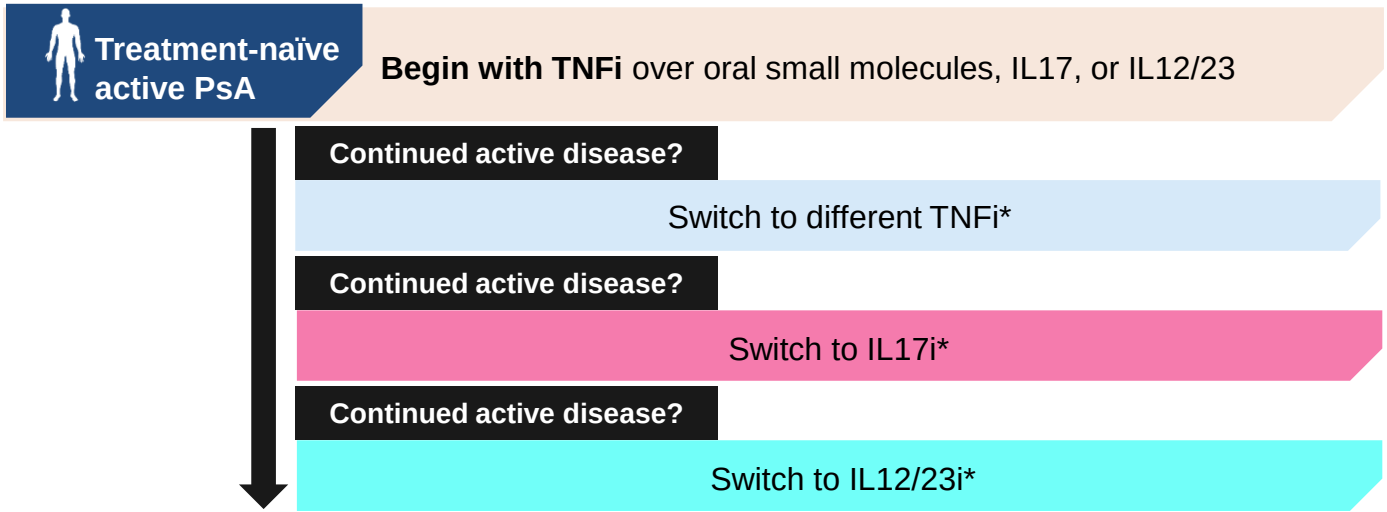
Part 3: Patient Specific Therapeutic Options

How do you approach treatment of PsA?

- Consideration of prominent domains
- Think about comorbidities
- Disease activity/severity
- Safety
- Patient preference

2019 ACR/NPF recommendations for **patients with active PsA**

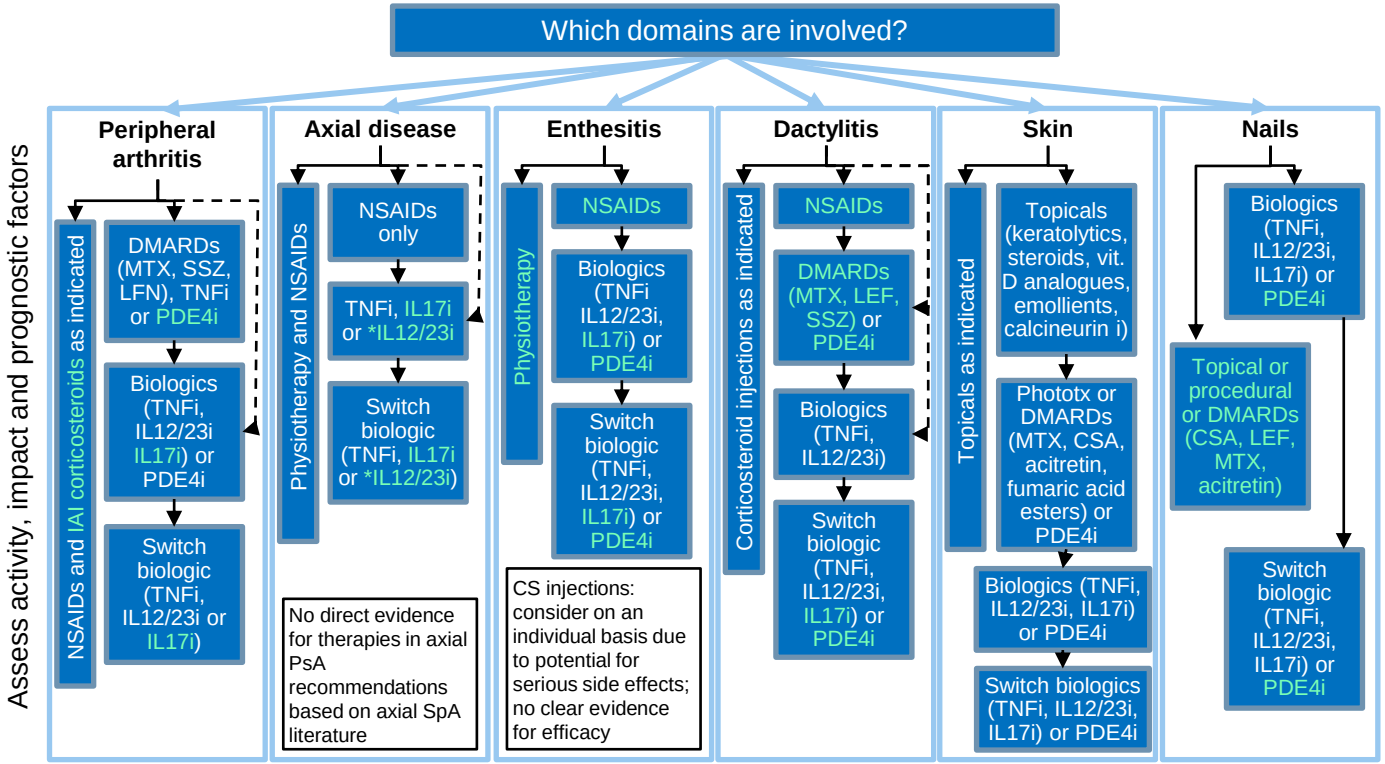


***Biologic therapy is recommended over biologic-with-MTX combination therapy.**

Methotrexate or other oral small molecules (OSMs) can be employed if indicated by cost or other reasons, depending on local situation with as monotherapy or in combination with biologics or TSDmards to bolster effect or combat immunogenicity.

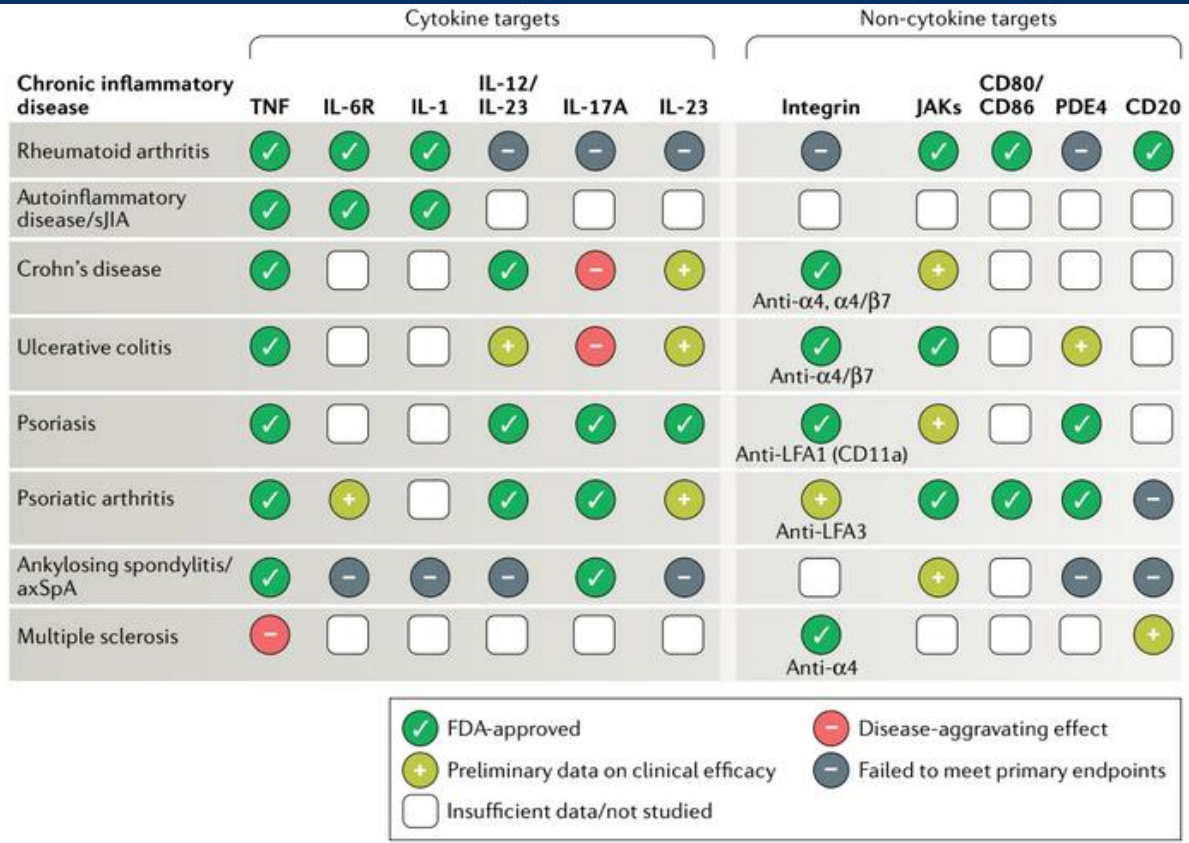
ACR. American College of Rheumatology; bDMARD, biologic disease-modifying antirheumatic drug; IL, interleukin; MTX, methotrexate; NPF, National Psoriasis Foundation; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor. Singh A, et al. *Arth Rheum* 2019;71;5–32.

GRAPPA PsA Tx Recommendations 2015



Coates L et al. *Arthritis Rheumatol* 2016;68:1060–71.

Targeted Therapies in Chronic Inflammatory Disease



Bravo, A., Kavanaugh, A. Bedside to bench: defining the immunopathogenesis of psoriatic arthritis. *Nat Rev Rheumatol* **15,** 645–656 (2019). https://doi.org/10.1038/s41584-019-0285-8

For your reference… Comorbidity recommendations

Comorbidity	NSAIDs	Glucocorticoids	Cyclosporine	Sulfasalazine	Methotrexate	Leflunomide	Hydroxychloroquine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab	Apremilast
CVD	C	?												
CHF	C	C						C	C	C	C	C		
Obesity					C									
Metabolic syndrome		C			C									
Diabetes		C			C									
Crohn's Disease	?			A	OL				A	A	A			
Ulcerative Colitis	?		OL	A					A	A		A		
Uveitis		P*						?	P	P				
Osteoporosis		C												
Fatty liver disease	C			C	C	C								
CKD	C		SM		C	?								
Depression														?
Chronic HepB†	C				C	C		SM	SM	SM	SM	SM	?	
Chronic HepC†	C				C	C		? P	?	?	?	?	?	
HIV								SM	SM	SM	SM	SM	?	
Malignancy								C	C	C	C	C	?	

C Caution
? Data insufficient, concerns raised
A Approved for primary therapy
OL Off-label use
P Preferred therapy
SM Requires special monitoring

Table adapted from Coates 2016[1]

*Corticosteroids used as preferred therapy for uveitis are most commonly given as topical and/or intraocular injections in preference to oral steroids. †When treating patients with chronic infections that can affect the liver, consider consultation with providers having expertise in the area. CVD, cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; HepB, hepatitis B; HepC, hepatitis C; HIV, human immunodeficiency virus; NSAIDS; non-steroidal anti-inflammatory drugs.

1. Coates L, et al. Arthritis Rheumatol. 2016;68:1060–71.

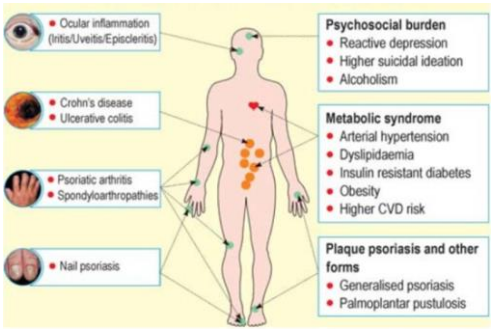
PsA Therapeutic Groups

- Conventional synthetic DMARDs (cs-DMARDs)
  - Methotrexate, Sulfasalazine, Leflunomide
- TNF inhibitors (TNFi)
  - Etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), certolizumab (Cimzia)
- IL17i
  - Secukinumab (Cosentyx), ixekizumab (Taltz), Bimekizumab
- IL12/23i
  - Ustekinumab (Stelara)
- IL23i
  - Guselkumab (Tremfya), Risankizumab (Skyrizi), Tildrakizumab (Ilumya)
- T cell modulator
  - Abatacept (Orencia)
- Targeted synthetic DMARDs (ts-DMARDs)
  - PDE4i (Apremilast (Otezla))
  - JAKi (tofactinib (Xeljanz), Baricitinib (Olumiant), Upadacitinib (Rinvoq), filgotinib)
  - Tyk2i

Mease P. *Ann Rheum Dis.* 2011; 70 (Suppl 1) 77-84
Mease P. *Rheum Dis Clin North Am.* 2015; 41: 723-38.

DRUGS and their **Pros** and **Cons**…

Patients don’t follow the algorithm!



Methotrexate

Is MTX effective in PsA?

- **MIPA Trial:** Double-blind, parallel-group randomized controlled trial (N = 221). Patients randomized to receive MTX (target dose 15 mg/week) or PBO.
  - Failed to show MTX improves inflammatory synovitis in PsA. No difference between groups at 3 or 6 months
- **TICOPA trial:** Study of T2T/tight control in early PsA.
  - Subanalysis showed MTX effective, ACR 20 – 41% at 12 weeks, improvement in dactylitis and enthesitis
- **Ineffective in the spine**

Kingsley GH, et al. *Rheumatology*. 2012;51:1368-1377.
Coates LC et al. EULAR 2015, Rome, #SAT0556

Methotrexate: Summary

PROs

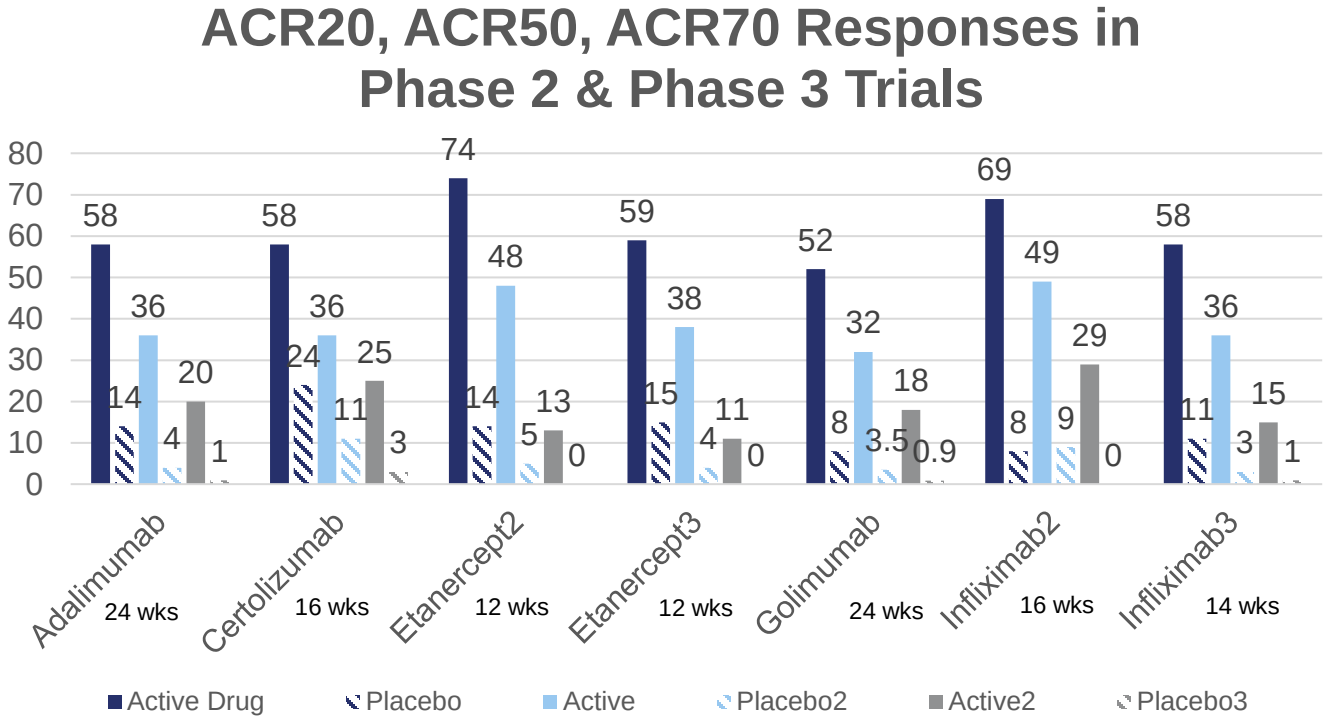
- Cheap
- Effective in mild disease
- May not need escalation
- Can help prevent Ab development in TNF blockers
- May increase efficacy in some biologics (studies in RA)

CONs

- Lab monitoring
- Patient tolerability
- Possible liver toxicity
  - Especially in patients with fatty liver disease
- Contraindicated in pregnancy

TNF Inhibitors (TNFi)

TNFi Therapies in PsA: ACR Responses



Mease et al. Lancet 2000;356:385-90; Antoni et al, A8R 2005; 52:1227; Mease et al. A&R 2004;50:2264-72; Antoni et al. ARD 2005; 64:1150; Mease et al A&R 2004; 50:2264; Mease et al, ARD 2005; 52:3279; Kavanaugh et al. Arthritis Rheum 2007; Mease et al, EULAR 2012

Anti-TNFs in PsA: Summary

PROs

- Effective in all 5 domains:
  - ~60% PASI 75 response with monoclonal constructs (-mabs); lesser with soluble receptor (Enbrel)
  - Enthesitis: ~60-75% improvement
  - Dactylitis:~60% improvement
- Effective in IBD
  - Exception Enbrel, others more specific to Crohn's or UC
- Effective in uveitis, although only Humira has FDA approval
  - Exception Enbrel
- Pregnancy safety data – Cimzia
  - But Enbrel thought to be safe

CONs

- Black box warning lymphoma
- Possibly trigger, exacerbate other autoimmune disease (MS, Lupus)
  - Don't use in patients with +dsDNA!
- Increased risk for non-melanoma skin cancer
- Generally, a bit higher risk for serious infections

Mease P. Ann Rheum Dis. 2011;70:77-84; Mease P. Arth Care & Research. 2011:63;64-85

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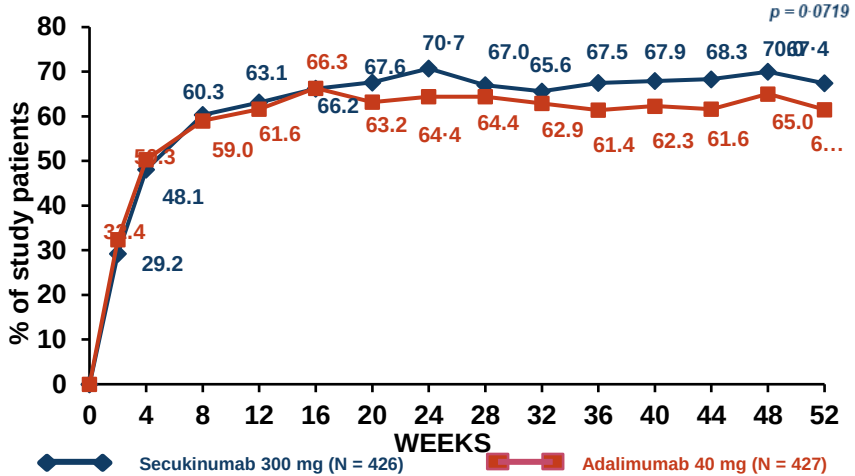
IL-17i

EXCEED Trial: H2H Secukinumab vs Adalimumab

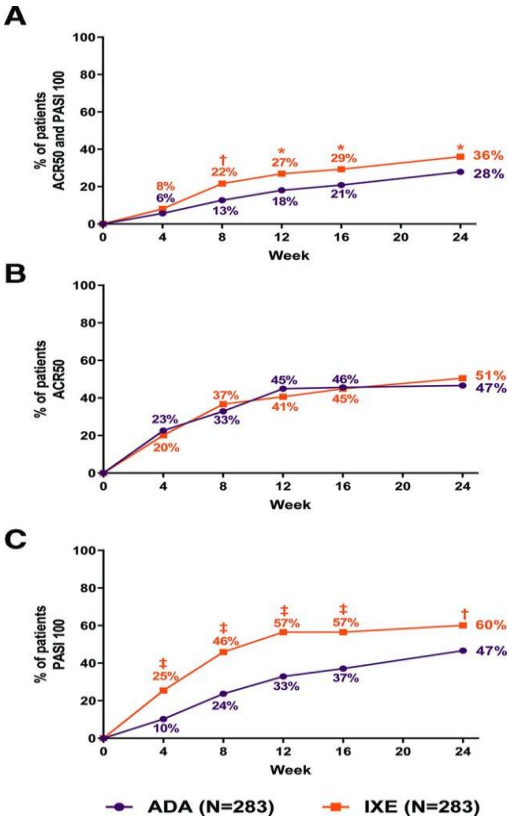
- **EXCEED,** double-blind trial in PsA
- Secukinumab similar to adalimumab in speed and magnitude of effect in musculoskeletal domains: arthritis, enthesitis, dactylitis
- Secukinumab **superior to adalimumab in skin response**
- Secukinumab demonstrated a higher retention rate at 52 weeks
- Safety profile of both medications consistent with known safety of each profile

ACR 20 Response at week 52
Primary endpoint



McInnes IB, Behrens F, Mease PJ, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet. 2020;395(10235):1496-1505.

SPIRIT Trial:
H2H – Ixekizumab vs Adalimumab



Mease PJ, et. al. Ann Rheum Dis. 2020 Jan;79(1):123-131.

SPIRIT Trial:

- Second H2H Trial in PsA, total of 566 pts
- Primary and all major secondary endpoints met. IXE was superior to ADA in combination ACR 50 and PASI 100 (see chart A).
- IXE was non-inferior to ADA in ACR 50 (see chart B)
- IXE was superior in PASI 100
- Nail improvement from baseline was superior over ADA
- Less serious infections in IXE (1.4%) vs. ADA (2.8%)

Clinical response rates for primary and major secondary outcomes through week 24 (non-responder imputation). (A) Percentage of patients simultaneously achieving ACR50 and PASI100 (primary endpoint). (B) Percentage of patients achieving ACR50 (major secondary endpoint). The treatment difference of IXE minus ADA was 3.9% (95% CI −4.3% to 12.1%). The lower bound of the 95% CI (−4.3%) was greater than −12%, thus meeting noninferiority criteria. (C) Percentage of patients achieving PASI100. IXE versus ADA: *P<0.05, †p<0.01, ‡p<0.001. ACR, American College of Rheumatology; ADA, adalimumab; IXE, ixekizumab; PASI, Psoriasis Area Severity Index

IL-17 Inhibitors: Summary

PROs

- Effective in all 5 domains
  - **Non-inferior** in joints vs TNFs
  - **Better in skin** vs TNFs
  - **Better in nails** vs TNFs
  - **Effective** in the Spine
- Less serious infection risk than TNF's
- No black box warning

CONs

- May exacerbate IBD
- Slightly higher risk for *candida infections*
- Appear to have no benefit in uveitis

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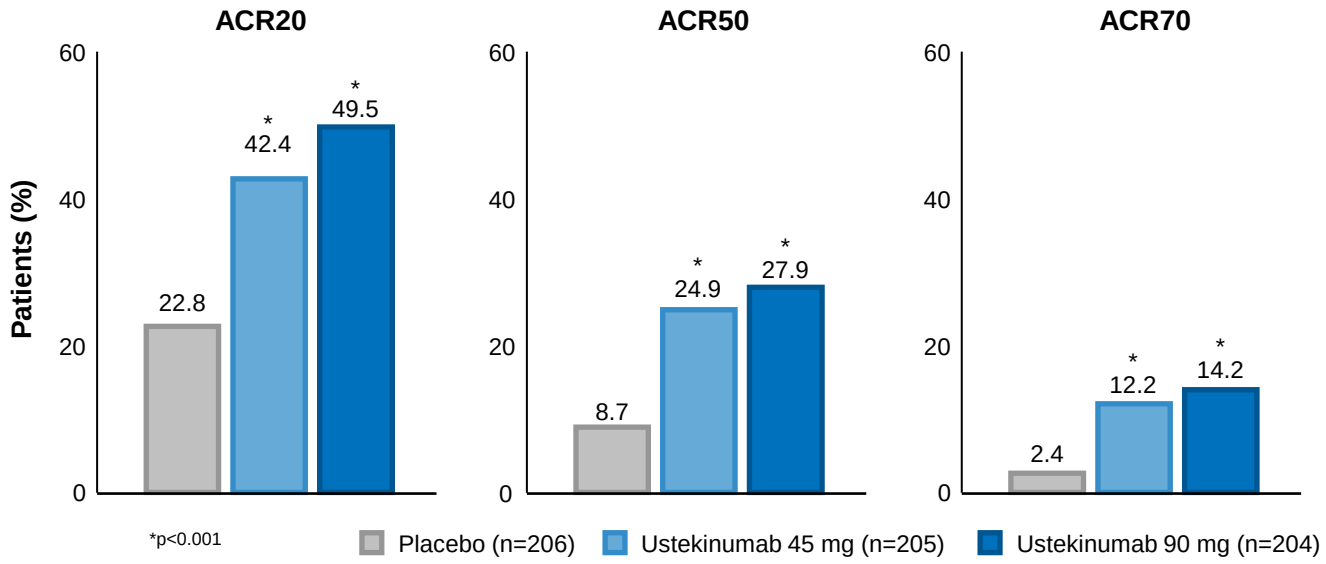
IL-12/IL-23i

Ustekinumab: PSUMMIT I trial

Treatment response at Week 24

PSUMMIT I



McInnes IB et al. Lancet 2013; 382(9844);780-9.

Ustekinumab (Stelara): Summary

PROs

- Effective in 4 Domains
- Better efficacy in enthesitis than TNFi (ECLIPSA study)
- Effective in Crohn’s and UC
- Dosing schedule

CONs

- Ineffective in spine (failed axSpa trials)
- Typically less effective in joints

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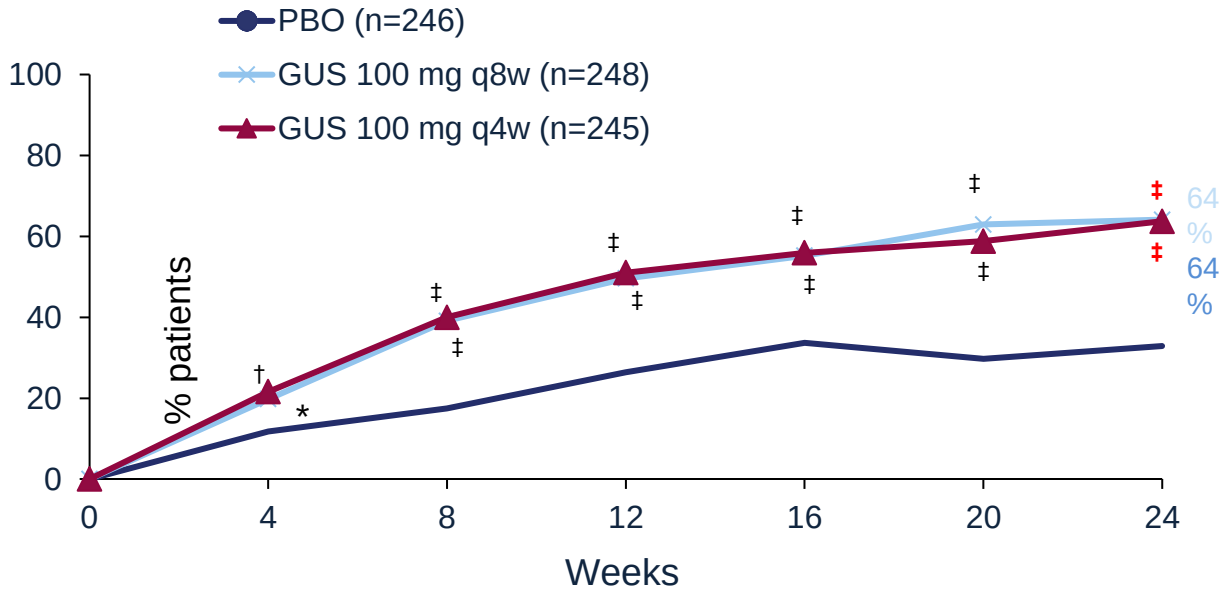
IL-23i

DISCOVER 2 Trial:
Guselkumab - ACR 20 response over time



*P<0.05; †P<0.01; ‡P<0.001 vs PBO, unadjusted (nominal); **bold** = adjusted

Phase 3: RDBPCT in 739 biologic-naïve patients with active PsA despite non-biologic DMARDs and/or NSAIDs

Discover 2 Trial
Key Secondary endpoints

	GUS 100mg Q 4 weeks	GUS 100mg Q 8 week	Placebo
Resolution of Dactylitis** t	101/159 (64%)	96/160 (59%	65/154 (42%)
Resolution of Enthesitis** t	109/243 (45%)	114/230 (50%)	75/255 (29%)
PASI 90 at wk 24*	112/184 (61%)	121/176 (69%)	18/183 (10%)
MDA at wk 24	46 (19%)	62 (25%)	15 (6%)

**<0.0001 Unadjusted (nominal) p values are not controlled for multiplicity and should be interpreted only as supportive. ACR20=American College of Rheumatology 20% improvement. ACR50=ACR 50% improvement. ACR70=ACR 70% improvement. DAS28-CRP=28-joint disease activity score based on C-reactive protein. HAQ-DI=health assessment questionnaire—disability index. PASI75=psoriasis area and severity index 75% improvement. PASI90=PASI 90% improvement. PASI100=PASI 100% improvement. vdHS=van der Heijde-Sharp. *Assessed in patients with at least 3% body surface area affected by psoriasis and investigator's global assessment of psoriasis score of at least 2 at week 0. [f] Pooled Discover 1 and Discover 2 dactylitis and enthesitis at wk 24.

Mease PJ,et. al DISCOVER-2 Study Group.Lancet. 2020 Apr 4;395(10230):1126-1136.

IL-23i: Summary

PROs

- Effective in 4 domains, possibly 5 (? Spine)
- Probably **best in skin** compared to other MOA's on market
- Tremfya improves fatigue
- Early studies suggest effective in **IBD**
- SAFE! Serious infection risk similar to placebo

CONs

- ? Efficacy in the spine
  - Risankizumab did not meet primary endpoint in proof of concept phase II AS study

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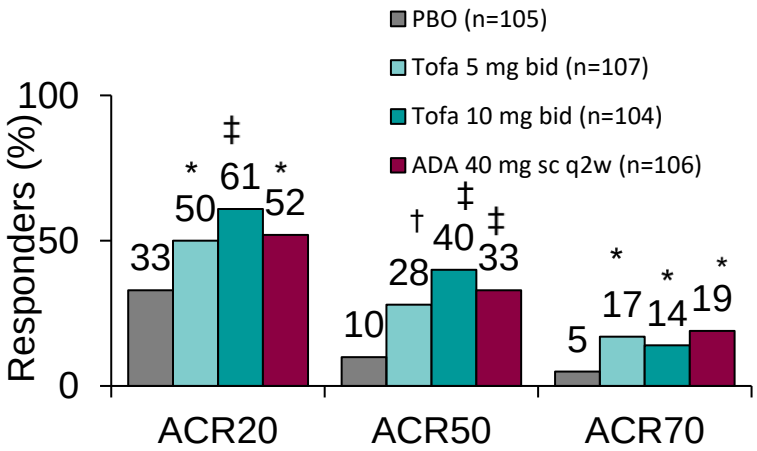
JAK Inhibitors

OPAL Broaden Trial Phase III (NRI): Tofacitinib (Xeljanz) in DMARD failures in PsA

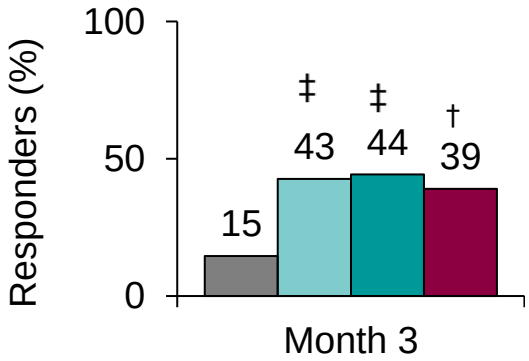
422 randomized TNFi-naïve pts, 88% concomitant MTX. 1° endpoints: Month 3 ACR20.

ACR Responders at month 3



*P≤0.05, †P<0.001, ‡P<0.0001 vs PBO at Month 3

PASI 75 Responders at month 3



Mease P, et al. N Engl J Med. 2017; 377: 1537-1550

JaK Inhibitors: Summary

PROs

- **Effective in all 5 Domains**
  (+ Phase II study in AS)
- Oral medication
- Short half-life
  - Consider for patients with h/o frequent infections
- Effective in UC
- Benefit in uveitis?

CONs

- Higher incidence of herpes zoster
  - Especially in Asian population
- Requires monitoring labs
- Can elevate cholesterol
- Higher risk of serious infections than IL-17s, IL-23s
- Contraindicated in pregnancy
- Increased risk of DVTs?

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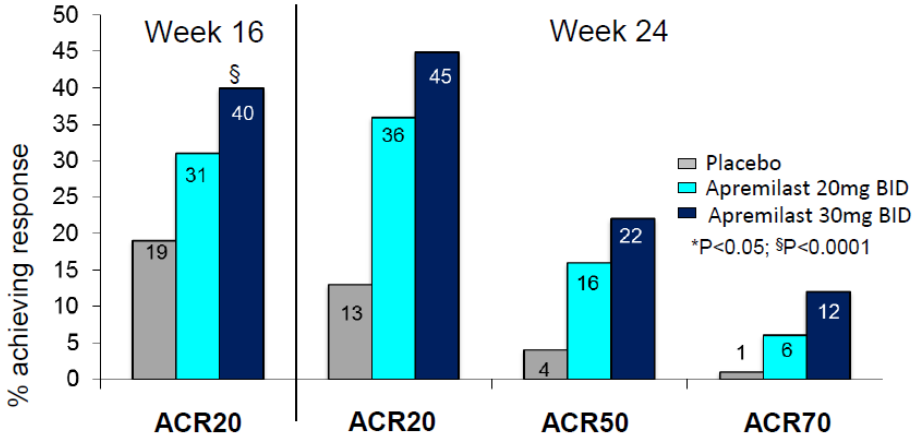
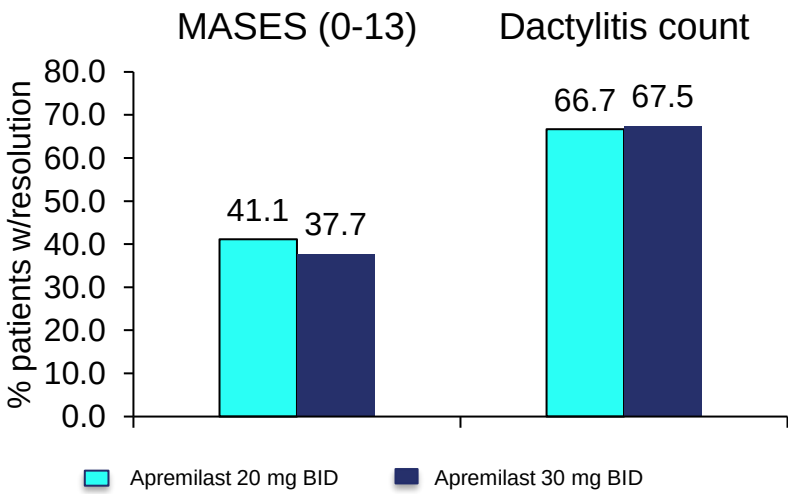
PDE-4 inhibitor

Apremilast (Otezla) effects on ACR response, enthesitis and dactylitis

PALACE 1



Data pooled from PALACE 1–3 Week 52



Kavanaugh A et al, ACR 2012, Washington, #L13
Gladman DD, et al Apremilast *Arthritis Rheumatol.* 2016; 68 (suppl 10).

Apremilast (Otezla)

PROs

- **No immunosuppression**
  - Good option for patients with recurrent infections
- **No laboratory monitoring**
  Moderate benefit on skin
  - PASI 75 at wk 16 – 40.9%
- Moderate benefit in arthritis, enthesitis and dactylitis
- ? Weight loss

CONs

- No radiographic data
- ACR responses not as robust compared to bDMARDs and sDMARD (Xeljanz)
- Nausea/diarrhea common initially
- Possible increase in depression
  - (1.2% vs 0.8%)
- Ineffective in the spine

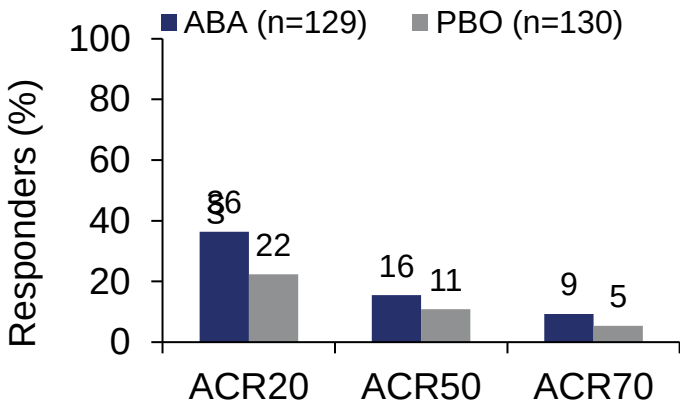
Kavanaugh et al, arthritis Res Ther 2019;21:118

Abatacept (Orencia) in Treatment of active PsA: Phase III Trial

213 ABA 125 mg sc weekly vs 211 PBO (PBO 24 weeks → open-label ABA)

- 60% had prior TNF exposure
- Results at week 24:
  - PASI 75 – 18%
  - Enthesitis resolution – 33%
  - Dactylitis – 44%
  - Both enthesitis & dactylitis higher response by week 52 (15-20% higher in both)
- Combined ACR 20 – 39%*
- No unexpected safety findings relative to RA studies

TNFi-exposed ACR responders at Week 24

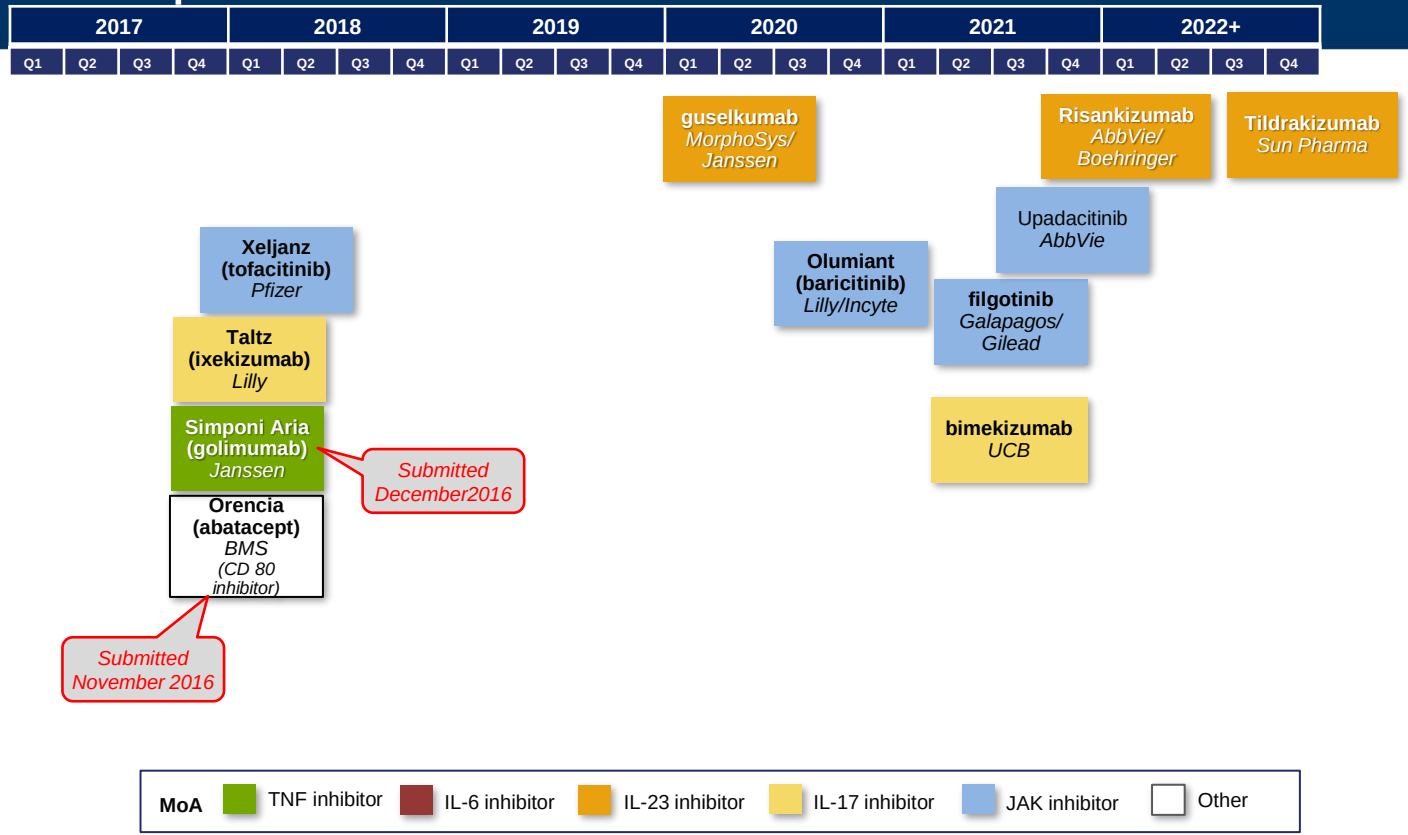


*P<0.001 vs PBO; †95% CI of estimate of difference in ACR50 response for ABA vs PBO did not cross 0 Nominal P-value 0.003‡, 0.012§ vs PBO. Nominal P-values were not calculated for ACR50/70

Mease P, et al. *Arthritis Rheum* 2011;**63**:939–48. Mease P, et al. Ann Rheum Dis. 2017; 76: 1550-1558

Drugs in the pipeline…

Projected US Approval Timeline for Key Compounds for the Treatment of PsA



Slide courtesy of Dr. Philip Mease

One to watch out for: Tyrosine Kinase 2 (TYK2)

Why do we care?: An ORAL medication that may be **better in skin**, while maintaining good joint efficacy, when compared to JAKi

- TYK2 is an intracellular kinase
- More specific for IL-23
- *Safety may be more favorable than pan-JAKi*
- Likely effective in IBD
- ? Effect on spondylitis
- **Deucravacitinib** (BMS-986165) is a novel oral agent that selectively inhibits TYK2
  - Currently in phase 2 trial (RDBPC) for PsA

ABSTRACT NUMBER: L03 Efficacy and Safety of Deucravacitinib (BMS-986165), an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Patients with Active Psoriatic Arthritis: Results from a Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial ACR Convergence 2020

In Summary

- Psoriatic arthritis is a multifactorial, heterogeneous disease
- When selecting treatment options, you should consider the patient as a whole
  - Active domains
  - Comorbidities
  - Patient preference

Additional References

Siannis F, Farewell VT, Cook RJ, jSchentag CT, Gladman DD. Clinical and radiographic damage in PsA. Ann Rheum Dis 2006;65(4):478.
Sieper J. Ann Rheum Dis 2009;68(Suppl II):ii1–ii44. doi:10.1136/ard.2008.104018
Chandran V, et al. Arthritis Rheum 2009;61:1235-42
ACR Convergence 2020. Philip Mease[1], Atul Deodhar[2], Désirée van der Heijde[3], Frank Behrens[4], Alan Kivitz[5], Jonghyeon Kim[6], Shalabh Singhal[6], Miroslawa Nowak[6] and Subhashis Banerjee[6], [1]Swedish Medical Center/Providence St. Joseph Health and University of Washington, Seattle, WA, [2]Oregon Health & Science University, Portland, OR, [3]Leiden University Medical Center, Leiden, Netherlands, [4]CIRI/Rheumatology and Fraunhofer Institute IME, Translational Medicine and Pharmacology, Goethe University, Frankfurt, Germany, [5]Department of Rheumatology, Altoona Center for Clinical Research, Duncansville, PA, [6]Bristol Myers Squibb, Princeton, NJ

Thank you!