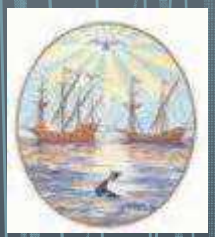
APso



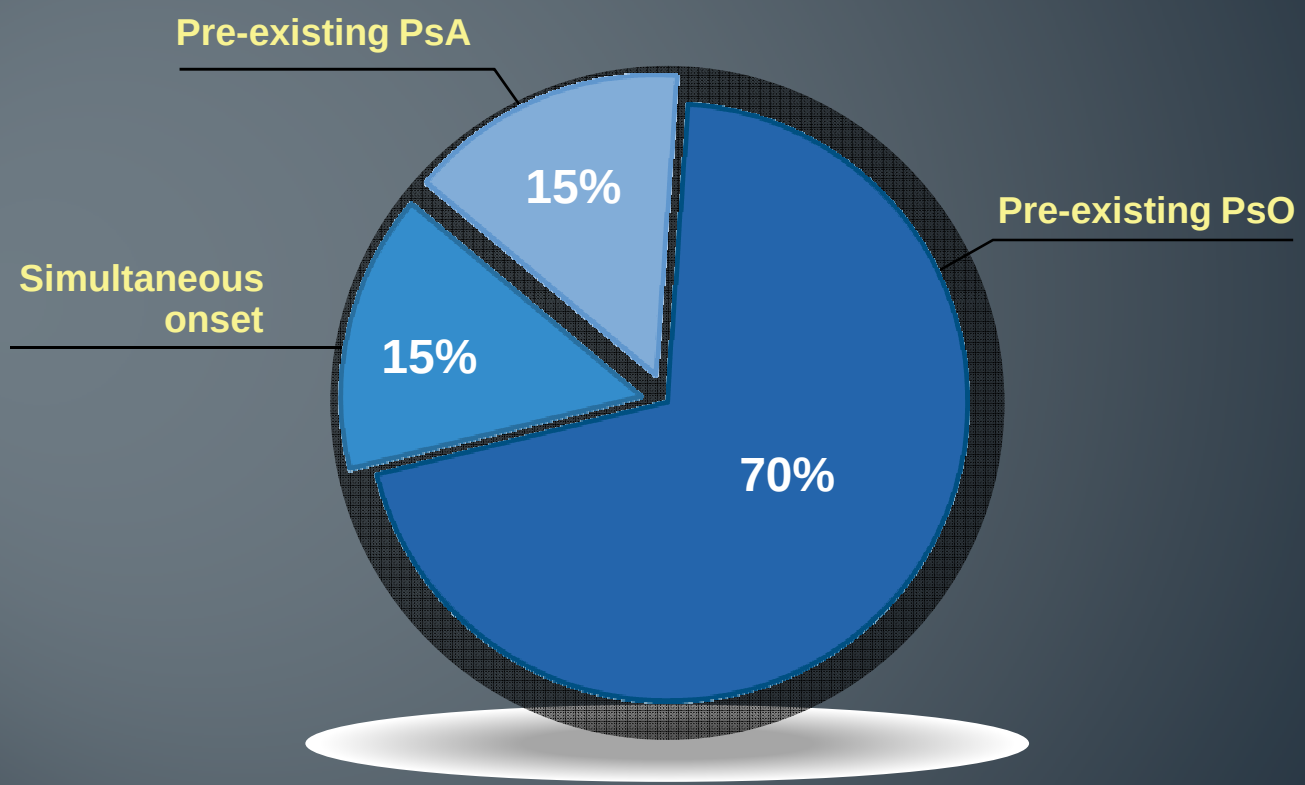
Prof. Dr. Juan José Scali
Unidad Academicade Reumatología,
Autoinmunidad y Osteologia
Hospital Carlos Durand, Bs As

Epidemiologia de PsA

- Prevalencia estimada de PsA en sujetos con psoriasis activa es 25% (6–42%), mientras la verdadera prevalencia es desconocida[1-3]
- Tipico comienzo acaece en pacientes 30–50 a de edad[4]
- Lesiones de piel preceden el comienzo de PsA en un promedio de 10a en aproximadamente 70% de pts[5]
- PsA puede preceder al desarrollo de psoriasis en una pequena proporcion de pacientes[5]
- Comienzo simultaneo de ambas formas PsAe y psoriasis occurre en 11–15% de sujetos[5]
- Hombres y mujeres igualmente afectados[6]

1. Gladman DD, et al. Ann Rheum Dis. 2005;64(Suppl II):ii14-7; 2. Wilson FC, et al. Arthritis Care & Res. 2009;61:233-9; 3. Haroon M, et al. Ann Rheum Dis. 2013;72(5):736-40; 4. National Psoriasis Foundation. About psoriasis: Statistics. Available at: www.psoriasis.org/netcommunity/learn_statistics. Accessed May 14, 2013; 5. Mease P, Goffe BS. J Am Acad Dermatol. 2005;52:1-19; 6. Brockbank J, Gladman DD. Exp Opin Invest Drugs. 2000;9(7):1511-22.

Presencia de PsO de piel ala Presentacion de PsA



Anandarajah AP, Ritchlin C. Nat. Rev. Rheumatol. 2009;5:634-41.

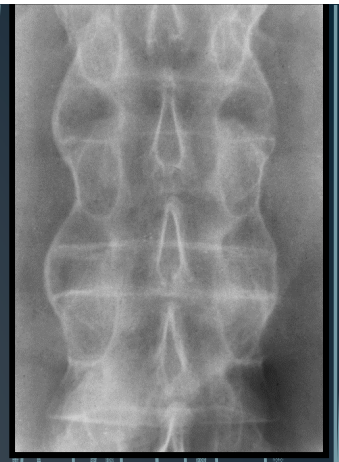
Mayores Hallazgos de PsA

Clinical	Laboratory	Radiographic
• Psoriasis of skin and nails	• Rheumatoid factor (RF) & Anti-citrullinated protein antibodies (ACPA) negative*	• Erosions and resorptions
• Peripheral arthritis	• Elevated Acute Phase**	• Joint space narrowing or involvement of entheseal sites
• Distal interphalangeal (DIP) involvement		• New bone growth at the enthesis
• Dactylitis		• Syndesmophytes***
• Enthesopathy		• Sacroiliitis***

*Low levels of RF and ACPA can be found in 5-16% of patients; **To a lesser degree than in RA; ***Spinal disease occurs in 40-70% of PsA patients

Helliwell PS & Taylor WJ. Ann Rheum Dis 2005;64(2:ii)3-8;
Fitzgerald "Psoriatic Arthritis" in Kelley's Textbook of Rheumatology, 2009

Mayores Hallazgos y su Frecuencia

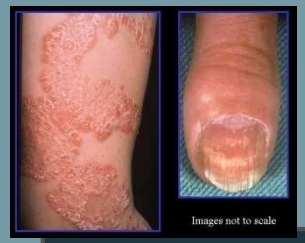


Compromiso lumbar (50%)[1]

Compromiso DIP (39%)[2]

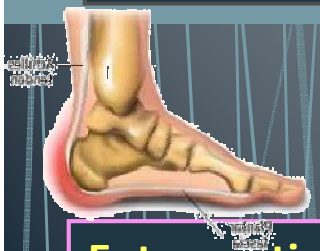
In nearly 70% of patients, cutaneous lesions precede the onset of joint pain, in 20% arthropathy starts before skin manifestations, and in 10% both are concurrent[6]

Compromiso de piel



Psoriasis ungueal (80%)[4, 5]

Dactilitis (48%)[3]

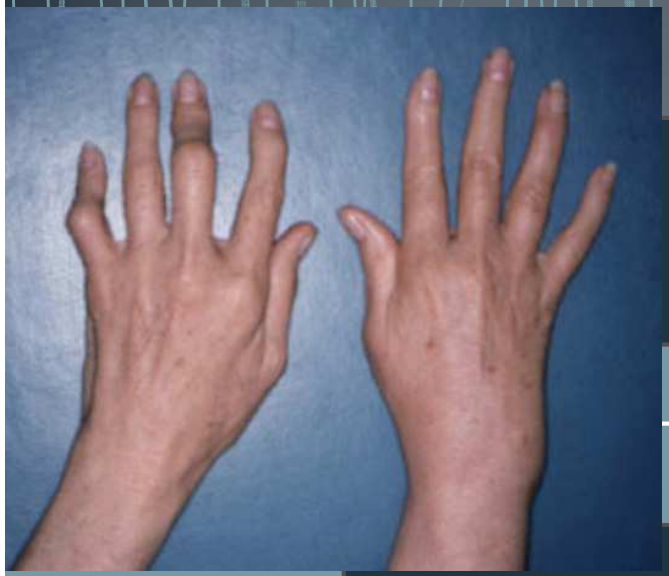


Entesopatia(38%)[2]

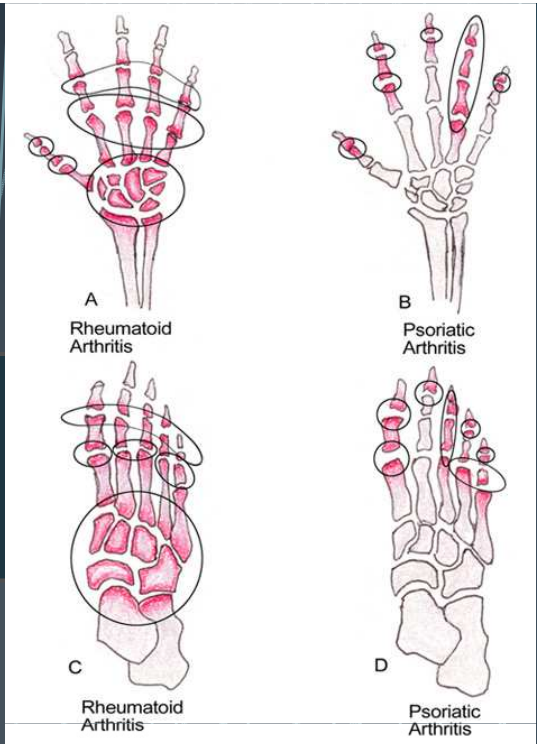
DIP: Distal Interphalangeal

[1]Gladman D, Husted JA, Tom BD, et al. Arth & Rheum 2007;56:840; [2]Kane D, Staffordy L, Bresnihan B, et al. Rheum 2003;42:1460-1468
[3]Brockbank J, Stein M, Schentag CT, et al. Ann Rheum Dis 2005;64:188–190; [4]Lawry M, Dermatol Ther 2007;20:60-67
[5]Jiaravuthisan MM, Sasseville D, Vender RB, et al. JAAD 2007;57:1-27; [6]Yamamoto T, Eur J Dermatol 2011;21:660-6

Hallmark Clinical Features in PsA

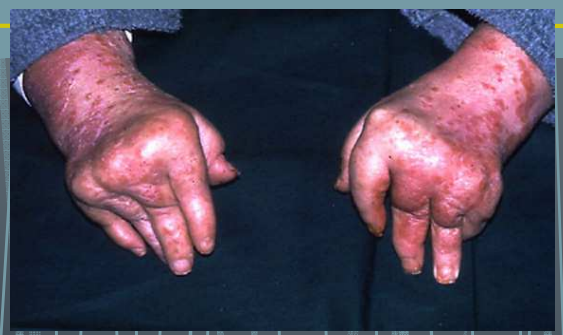


ArtritisPsoriatica



Dactilitis

Entesitis

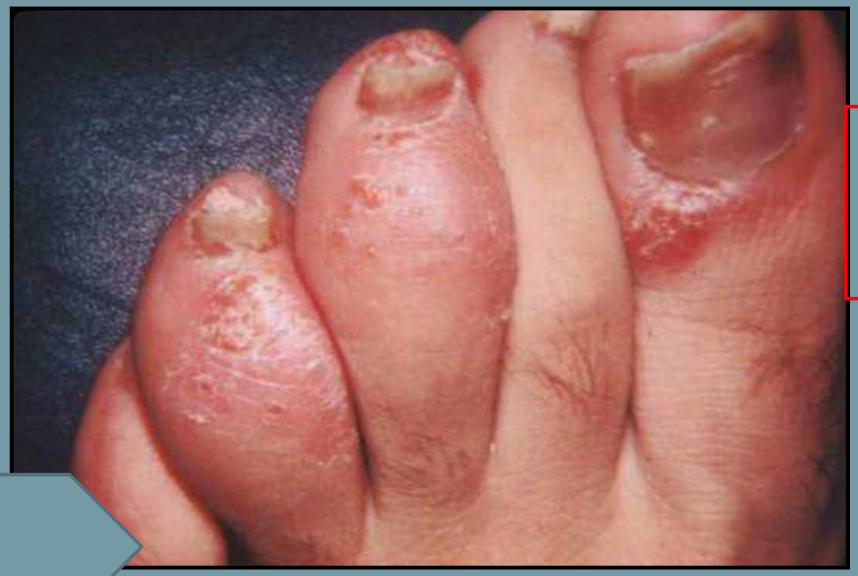


Ungueal

Ritchlin CT. J Rheumatol 2006;33:1435–1438;
Helliwell PS. J Rheumatol 2006;33:1439–1441;
Ash ZR, Tinazzi I, Gallegoet CC, et al. Ann Rheum Dis; Epub 09 December 2011

Dactilitis

- Inflamacion Difusa de un dedo puede ser aguda, con cambiosn inflamatorios dolorosos o cronicos mientras el dedo persiste hinchado a pesar de desaparecer la inflamacion aguda[1]



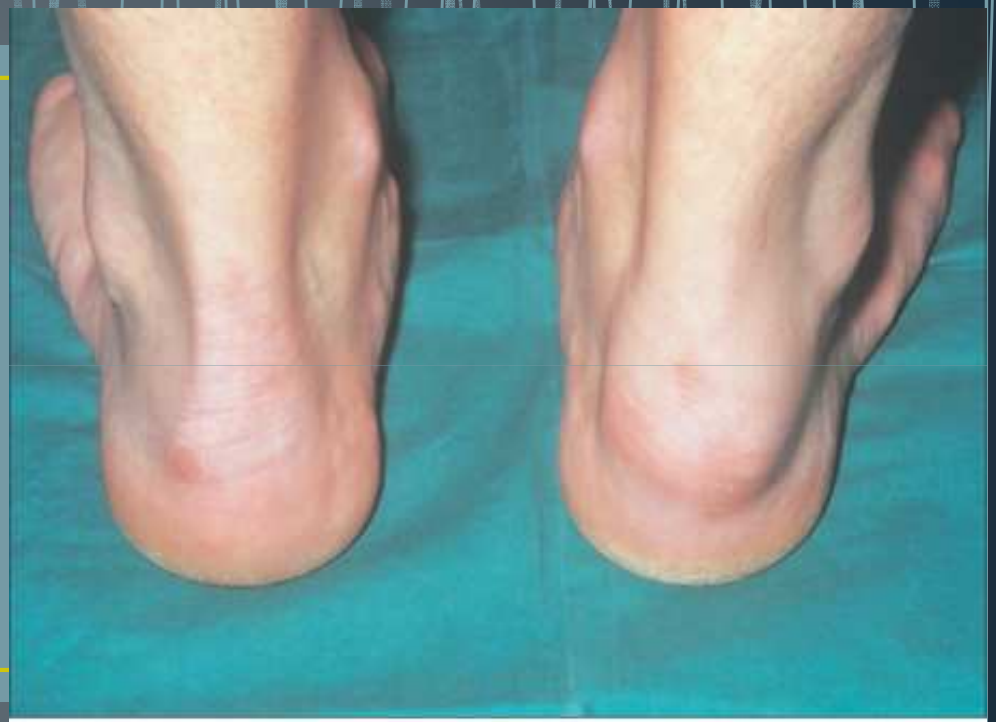
denominado dedo en salchicha"[1]

- Reconocido como uno de los hallazgos cardinales de PsA, occurriendo en **40% de pts**[1,2]
- Pies afectados mas communmente[1]
- Dactilitis involucrando dedos muestran mayor dano radiografico[1]

[1]Brockbficon M, Schentag CT, et al. Ann Rheum Dis 2005;64:188–190;
[2]Veale D, Rogers S, Fitzgerald O, et al. Br J Rheumatol 1994;33:133–38

Entesitis

- **Entheses** are the regions at which a tendon, ligament, or joint capsule attaches to bone[1]
- **Inflammation at the entheses is called enthesitis** and is a hallmark feature of PsA[1,2]
- Pathogenesis of enthesitis has yet to be fully elucidated[2]
- Isolated peripheral enthesitis may be the only rheumatologic sign of PsA in a subset of patients[3]



© www.rheumtext.com - Hochberg et al (eds)

- **Entesis: disipan el stress biomecanico y estan sujetos a repetidos traumas**

[1]McGonagle D. Ann Rheum Dis 2005;64(Suppl II):ii58–ii60;
[2]Anandarajah AP and Ritchlin CT, et al. Curr Opin Rheumatol 2004;16:338–343;
[3]Salvarani C, Cantini F, Olivieri I, J Rheumatol 1997;24:1106–1140

Treatment of the Nail Disease

Why is it important?

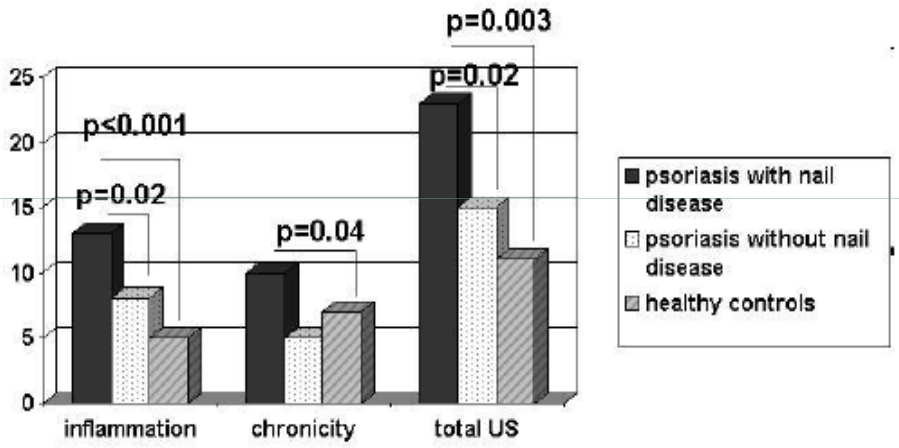
- Difficult to treat, slow to heal[1-3]
- >50% of patients suffer from pain[4]
- Restricts patients in daily activities and causes social embarrassement[4]
-

DIP involvement is secondary to nail disease[1]

[1]Scher RK. Dermatol Clin 1985;3:387-394;
[2]de Berker D, Clin Exp Dermatol 2000;25:357-362;
[3]Farber EM, Cutis 1992;50:174-178;
[4]de Jong EM, et al. Dermatology 1996;193:300-303

La Importancia de tratar la Psoriasis Ungueal

Figure 1: Comparison of median US scores related to inflammation and chronicity in psoriasis patients with and without nail disease and healthy controls.



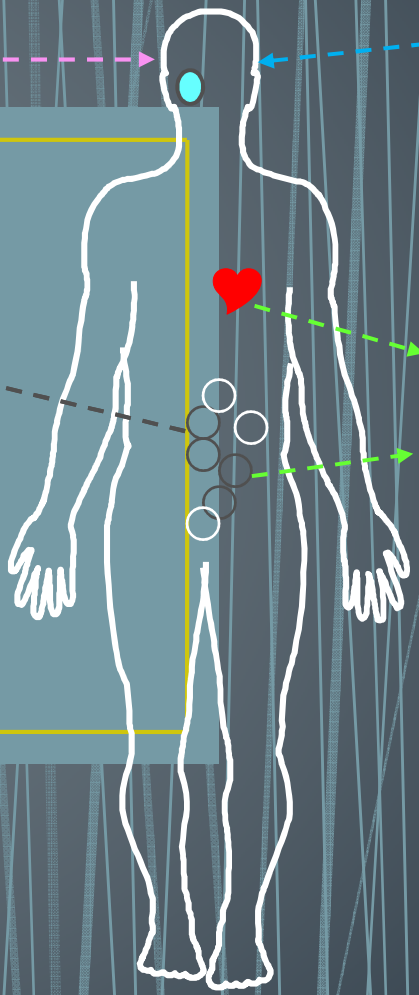
- Psoriasis patients with nail disease have a greater magnitude of underlying subclinical enthesopathy than Pso patients with normal nails
- More extensive nail involvement correlated with more severe enthesopathy scores
- These results will offer a
- novel anatomical basis
- for the predictive value
- of nail Pso for PsA
- evolution

Ash ZR, Tinazzi I, Gallegoet CC, et al. Ann Rheum Dis; Epub 09 December 2011; doi: 10.1136/annrheumdis-2011-200478

Comorbilidades en Pacientes conPsA

Ocular inflamacion[1]
(Iritis/Uveitis/ Episcleritis)

IBD



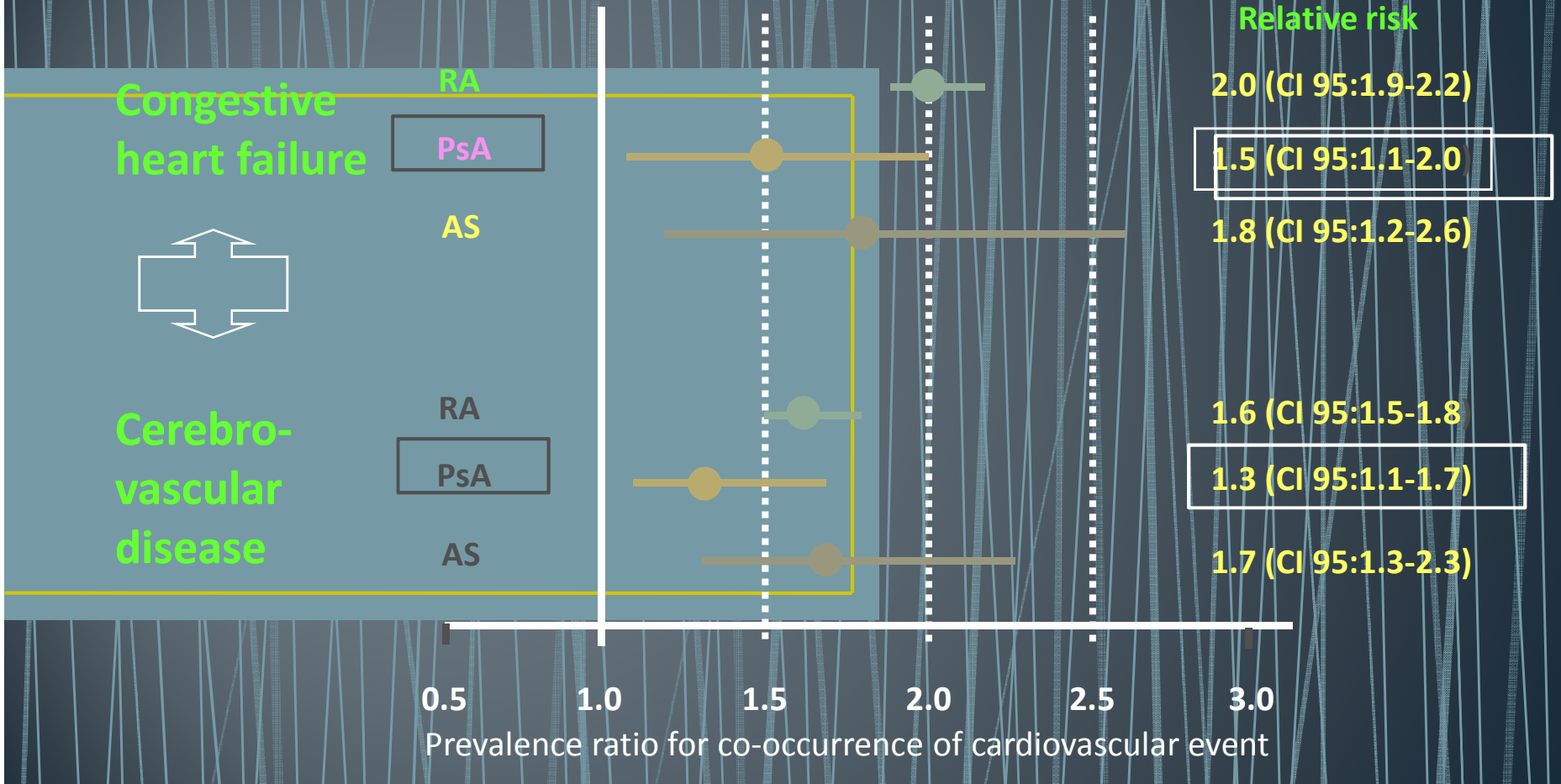
Pso patients[6-8]
- Psychosocial burden
- Reactive depression
- Higher suicidal ideation
- Alcoholism

Metabolic Syndrome[3-5]
- Hyperlipidemia
- Hypertension
- Insulin resistent
- Diabetes
- Obesity

⇒ Higher risk of cardiovascular disease (CVD)

[1]Qieiro R, Torre JC, Belzunegui J, et al. Semin Arth Rheum 2002;31:264; [2]Scarpa R, Manguso F, Arienzo AD, et al. J Rheum 2000;27:1241; [3]Mallbris L, Richtlin CT and Stable M, et al. Curr Rheum Rep 2006;8:355; [4]Neimann AL, Shin DB, Wang X, et al. J Am Acad Derm 2006;55:829; [5]Tam LS, Tomlinson B, Chu TTW, et al. 2008;47:718; [6]Kimball AB, Jacobson C, Weiss S, et al. Am J Clin Dermatol 2005;6:383-392; [7]Naldi L, Parazzini F, Brevi A, et al. Br J Dermatol 1992;127:212-217; [8]Mrowietz U, Elder JT, and Rarker J, et al. Arch Dermatol Res 2006;298(7):309-319

Elevado riesgo Cardiovascular en enf. Inflamatorias

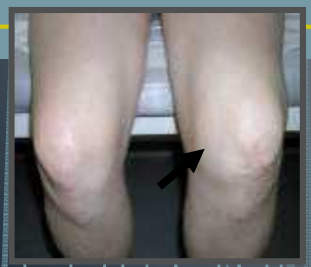


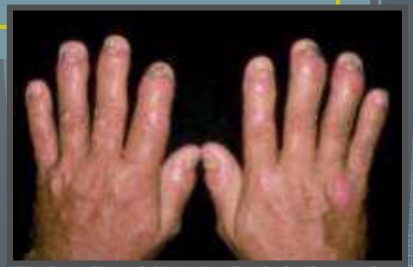
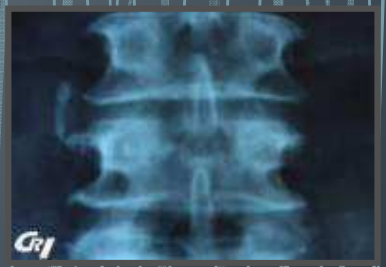
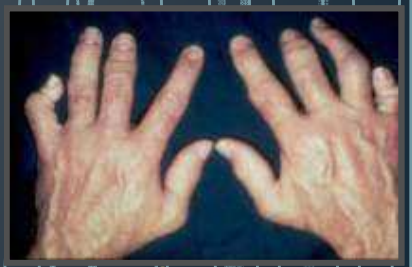
Also significant increase in risk for ischemic heart disease, atherosclerosis (except AS and PsA), peripheral vascular disease, hypertension, hyperlipidaemia, and Type II diabetes (except AS)

Han C, Robinson DW, Hackett MV, et al. J Rheumatol 2006 Nov;33(11):2167-72

Descripcion Clasica de PsA Usando los Criterios Diagnosticos de Moll and Wright

- **Incluyen 5 patyrones clinicos:**
  - Asymmetric mono-/oligoarthritis (~30% [range 12-70%])[1-4]
  - Symmetric polyarthritis (~45% [range 15-65%])[1-4]
  - Distal interphalangeal (DIP) joint involvement (~5%)[1]
  - Axial (spondylitis and Sacroiliitis) (HLA-B27) (~5%)[1,3]
  - Arthritis Mutilans (<5%)[1,3]

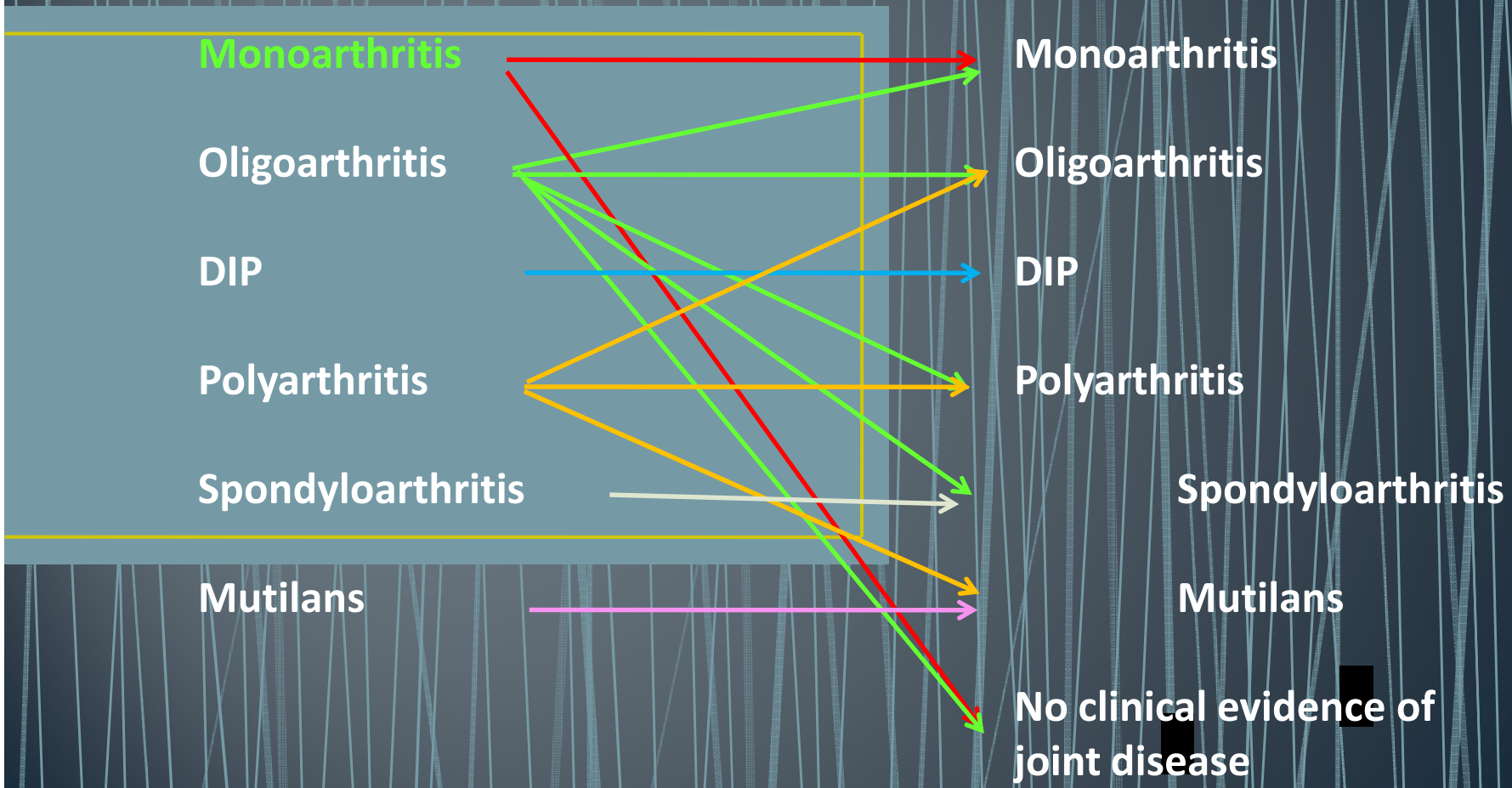


- Sin embargo los poatrones pueden cambiar en el tiempo y por ello ,no son utiles para clasificacion[5]

Patterns may Change Over Time and are Therefore not Useful for Classification

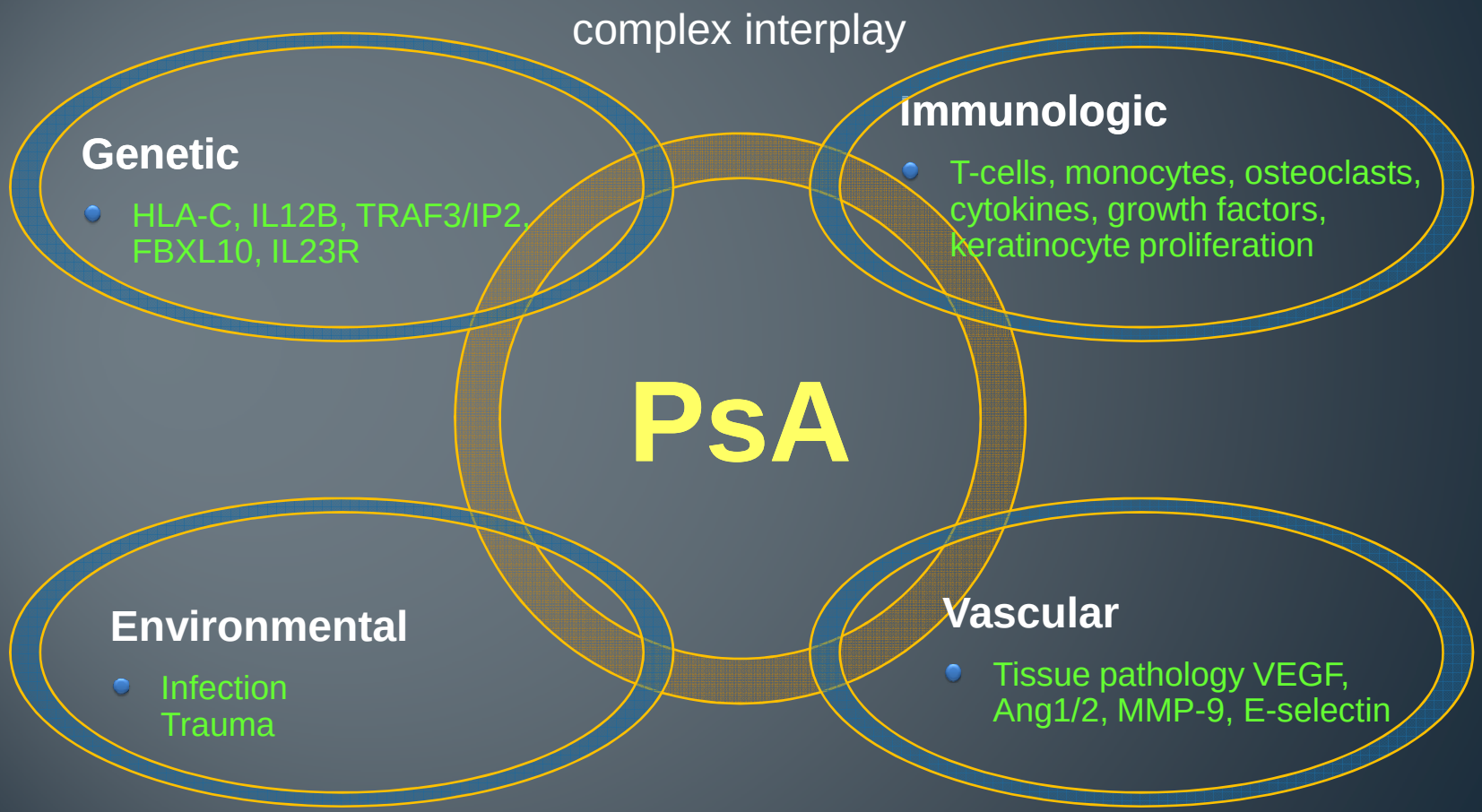
Clinical subgroups at baseline and follow-up:



McHugh N, Balachrishnan C, Jones SM, et al. Rheum 2003;42:778-783

Pathogenesis

Factores contribuyendo al desarrollo de PsA[1-6]



Adapted from: 1. Gladman DD. Curr Opin Rheum. 2002;14:361-6; 2. Liu Y, et al. PLoS Genet. 2008;4(3):e1000041;
3. Huffmeier U, et al. Nat Genet. 2010;42(11):996-9; 4. Stuart PE, et al. Nat Genet. 2010;42(11):1000-4;
5. Rahman P, et al . J Rheumatol. 2009;36:137-40; 6. Gao W, et al. Ann Rheum Dis. 2012. EPub Nov 17.

Predisposicion Genetica para PsA:evidencias

- Concordance is 35–70% in monozygotic twins versus 12–20% in dizygotic twins[1-4]
- First-degree relatives of PsA patients have a 40- to 50-fold increased risk of disease[3,5,6]
- Fathers with PsA are two times more likely to transmit the disease versus affected mothers[7]

1. Ortonne JP. Br J Dermatol 1999;140(Suppl 54):1-7; 2. Bhalerao J, Bowcock AM. Hum Mol Genet. 1998;7:1537-45; 3. Hohler T, Marker-Hermann E. Curr Opin Rheumatol 2001 ;13:273-9; 4. Henseler T. J Am Acad Dermatol 1997;37:S1-11; 5. Swanbeck G, et al. Br J Dermatol. 1997;137:939-42; 6. Karason A, et al. Rheumatology (Oxford). 2009;48(11):1424-8; 7. Rahman P, et al. Arthritis Rheum. 1999;42(6):1228-31.

Genome-wide association studies (GWAS) in PsA

- **Susceptibility loci identified by GWAS include:[1-4]**
  - **HLA-C(**HLA-Cw6 was associated with a significantly earlier onset in PsA patients who carried the HLA-Cw*0602 allele.5)
  - **IL12B**
  - **TRAF3/IP2***
  - **FBXL10**
  - **IL23R**
- **GWAS studies in PsA have so far used small samples – it is likely that more PsA genes are yet to be found[5]**
- **PsA is genetically distinct from rheumatoid arthritis, suggesting different mechanisms of action for the two diseases[5]**

* Gene product ACT1 is pro-inflammatory via IL-17.

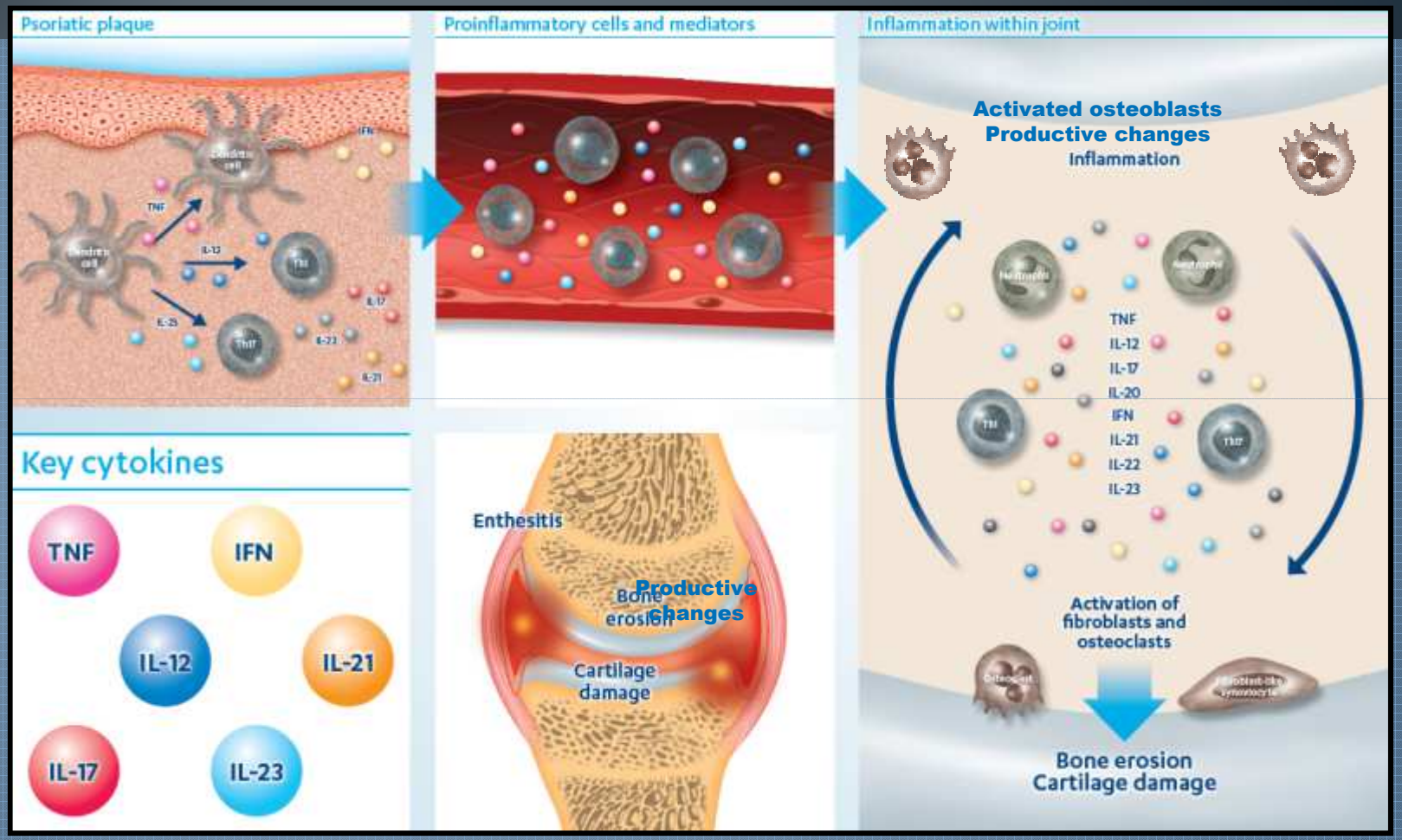
1. Liu Y, et al. PLoS Genet. 2008;4(3):e1000041; 2. Huffmeier U, et al. Nat Genet. 2010;42(11):996-9;
3. Stuart PE, et al. Nat Genet. 2010;42(11):1000-4; 4. Rahman P, et al . J Rheumatol. 2009;36:137-40;
5. Bluett J, Barton A. Curr Rheumatol Rep. 2012;14(4):364-8.

PsA is a polygenic disorder associated with different immunogenotypes

- MHC gene loci associations with PsA include:[1-4]
  - Class I alleles (HLA-B13, B17, B27, B38, B39, B57, Cw6)
  - Class II alleles (DR4)
- HLA-Cw6 is associated with early onset[5]
- HLA-B27, B39 and TNF-α-308 alleles are associated with disease progression[2,4]

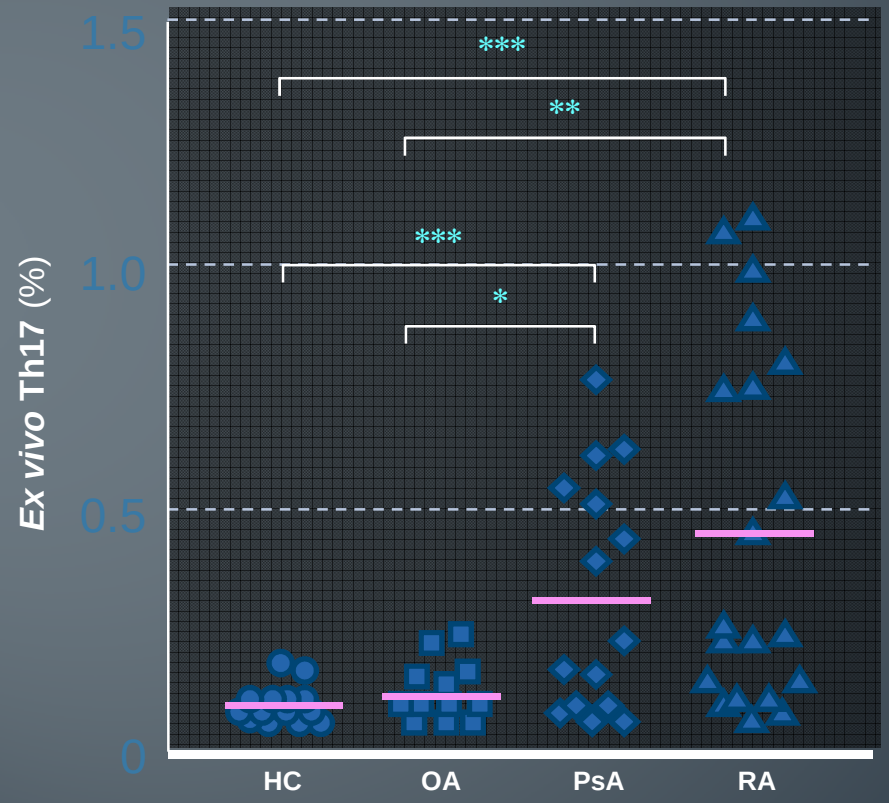
1. Veale DJ, Fitzgerald O. Clin Exp Rheumatol. 2002;20(Suppl 28):S27-33; 2. Anandarajah AP, Ritchlin CT. Curr Opin Rheumatol. 2004;16:338-43;
3. Gladman DD, et al. Hum Immunol. 2001;62:1239-44; 4. Korendowych E, et al. J Rheumatol. 2003;30:96-101;
5. Gladman DD, et al. Hum Immunol. 1999;60:259-61.

Patogenesis de PsA



Adapted from:
McInnes IB, Schett G. N Engl J Med. 2011;365(23):2205-19; Nograles KE, et al. Nat Clin Pract Rheumatol. 2009;5(2):83-91.
Maeda S, et al. Int J Rheumatol. 2012;2012:539683.

Patients with early active RA and PsA show increased Th17 levels in peripheral blood



* p<0.05
** p<0.01
*** p<0.001

HC: healthy control
OA: osteoarthritis
PsA: psoriatic arthritis
RA: rheumatoid arthritis

Leipe J, et al. Arthritis Rheum. 2010;62(10):2876-85.

Identifying the role of IL-12 and IL-23 in PsA

- Increased levels of IL-12/IL-23p40 have been reported in serum of PsA patients[1]
- In animal models (collagen-induced arthritis), IL-12/IL-23 is implicated in joint pathology:
  - IL-12/IL-23p40 knockout mice are resistant to arthritis induction[2]
  - Blockade of IL-12 reported to attenuate the severity of arthritis[3]
- Phase II data with anti-IL12/23 therapy have shown a positive impact on the skin and joint component of PsA[4]

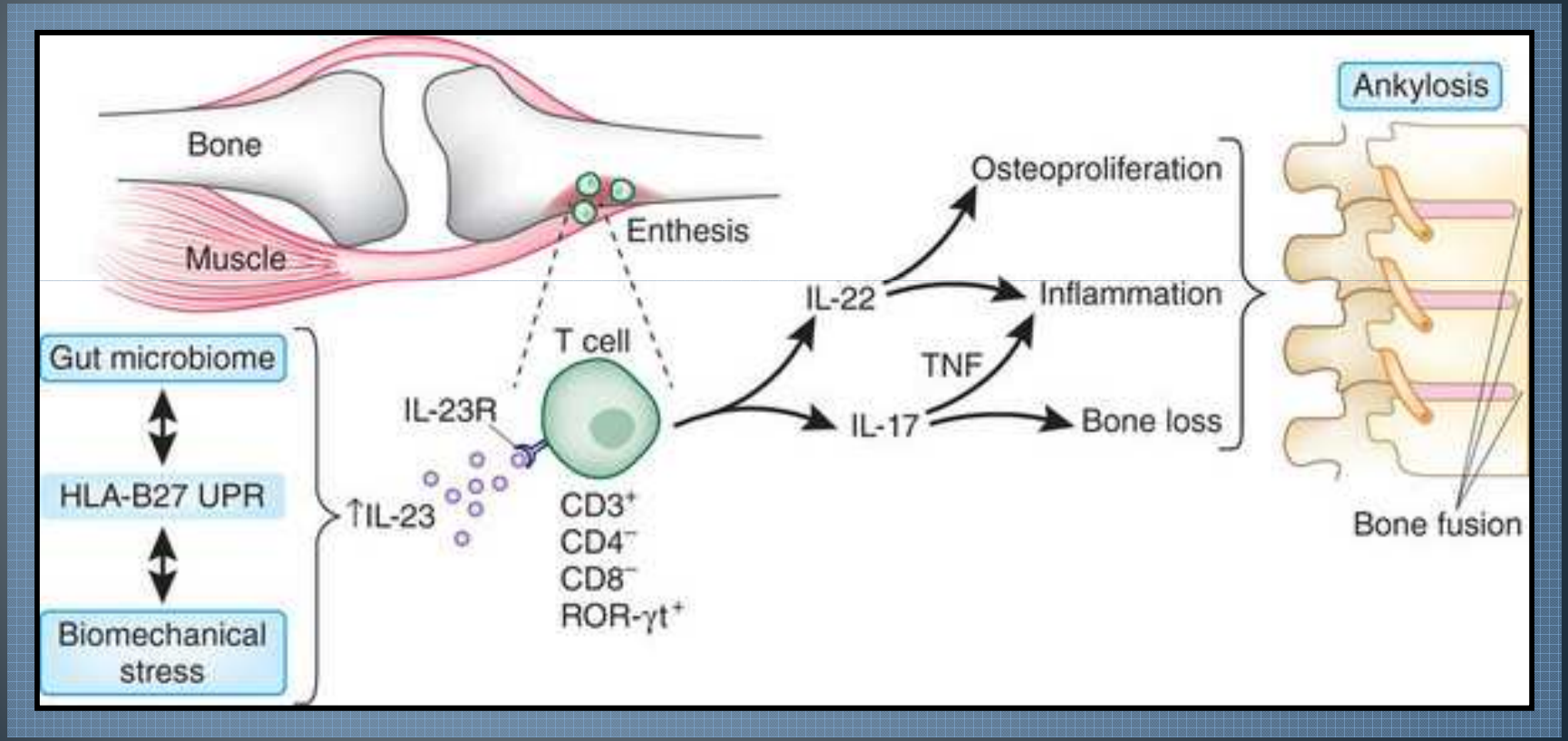
1. Szodoray P, et al. Rheumatology. 2007;46:417-25; 2. Murphy CA, et al. J Exp Med. 2003;198(12):1951-7.
3. Malfait AM, et al Clin Exp Immunol. 1998;111:377-83; 4. Gottlieb A, et al. Lancet. 2009;373(9664):633-40.

The role of IL-23 in spondyloarthritis (SpA)

- Recent findings have converged on the cytokine IL-23 as a key factor in spondyloarthritis
- Studies in mouse models have shown that IL-23:
  - Promotes highly specific entheseal inflammation by acting on a population of $CD3^{+}CD4^{-}CD8^{-}$ entheseal-resident lymphocytes, which produce IL-17 and IL-22
  - Is sufficient, in the absence of any other inflammatory signal, to reproduce the classical systemic features of spondyloarthritis
- Further insights into how IL-23 results in the distinct pattern of inflammation in spondyloarthritis are awaited

Sherlock JP et al. Nat Med. 2012 Jul 1;18(7):1069-76

Role of IL-23 and enthesis-resident T cells in disease development



Adapted from: Lories RJ, McInnes IB. Nat Med. 2012 Jul 6;18(7):1018-9.

Diagnostico de PsA

- Based on history, physical examination and radiographic features[1]
- Typically made in a patient with coexistence of arthritis (enthesitis/dactylitis/spondylitis) and psoriasis[1,2]
- No laboratory test is used to definitively diagnose PsA
  - Rheumatoid factor is usually negative[1]
  - ESR and CRP may be variably elevated[1]

1. Mease P, Goffe BS. J Am Acad Dermatol. 2005;52:1-19.
2. Taylor W, et al. Arthritis Rheum. 2006;54(8):2665-73.

Moll and Wright original diagnostic criteria(1973)

- The first developed classification of Psoriatic Arthritis and frequently used criteria in clinical studies[1,4]
  - Inflammatory arthritis*
  - Presence of psoriasis
  - Usually negative for RF
- Five overlapping clinical patterns described
  - Asymmetrical mono- or oligoarthritis (~30%) [1-4]
  - Symmetrical polyarthritis (~45%) [1-4]
  - DIP joint involvement (~5%) [1]
  - Axial (spondylitis and sacroiliitis) (~5%)[1,3]
  - Arthritis mutilans (<5%) [1,3]

*Peripheral arthritis and/or spondylitis

1. Moll JMH, Wright V. Semin Arthritis Rheum. 1973;3:55-78; 2. Gladman DD, et al. Q J Med. 1987; 62: 127-41;
3. Torre Alonso JC, et al. Br J Rheumatol. 1991;30:245-50; 4. Helliwell PS, Taylor WJ. Ann Rheum Dis. 2005;64(suppl 2):ii3-ii8

CASPAR criteria for PsA

Inflammatory articular disease (joint, spine, entheseal) with ≥3 points from:		Pts
1.	Current psoriasis (psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist).	2
	A personal history of psoriasis (a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider).	1
	A family history of psoriasis (history of psoriasis in a first- or second-degree relative according to patient report).	1
2.	Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.	1
3.	A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.	1
4.	Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.	1
5.	Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.	1

CASPAR - Classification criteria for Psoriatic Arthritis

Taylor W, et al. Arthritis Rheum. 2006;54(8):2665-73.

ASAS classification criteria for spondyloarthritis (SpA)

In patients with ≥3 months back pain and age at onset <45 years

Sacroiliitis on imaging plus 1 SpA feature	OR	**HLA-B27** plus 2 other SpA features

SpA features

- **Inflammatory back pain (IBP)**
- **Arthritis**
- **Enthesitis (heel)**
- **Uveitis**
- **Dactylitis**
- **Psoriasis**
- **Crohn's/colitis**
- **Good response to NSAIDs**
- **Family history for SpA**
- **HLA-B27**
- **Elevated CRP**

In patients with peripheral symptoms ONLY

Arthritis or enthesitis or dactylitis
plus

1 SpA feature

- **Uveitis**
- **Psoriasis**
- **Crohn's/colitis**
- **Preceding infection**
- **HLA-B27**
- **Sacroiliitis on imaging**

OR

2 other SpA features

- **Arthritis**
- **Enthesitis**
- **Dactylitis**
- **IBP ever**
- **Family history for SpA**

Rudwaleit M, et al. Ann Rheum Dis 2011;70:25–31.

Differential diagnosis

- Reactive arthritis (including Reiter's syndrome)[1-3]
  - Osteoarthritis[2]
  - RA[1,2]
  - Septic arthritis[1]
  - Gouty arthritis[1,2]
- Ankylosing spondylitis[2]
- Enteropathic arthritis[3]
- Other forms of spondyloarthritis

1. Leeb BF, et al. Dis Managed Health Outcomes. 1998;4(6):315-24; 2. Mease P, et al. J Am Acad Dermatol. 2005;52:1-19.
3. Khan M. Ann Intern Med. 2002;136(12):896-907.

Diagnostico

History

- **Psoriasis**
  - Active disease, or
  - Personal history, or
  - Family history
- **Swelling of joints**
  - Site of attachment of tendon to bone (e.g. Achilles joint inflammation)
  - Spinal inflammation (features of inflammatory BP/ limitation of movement)
- **Pain or tenderness in joints**
- **Morning stiffness >30 minutes**
- **Impaired functional capacity in activities of daily living**
  - Changes in ability to function at home and at work

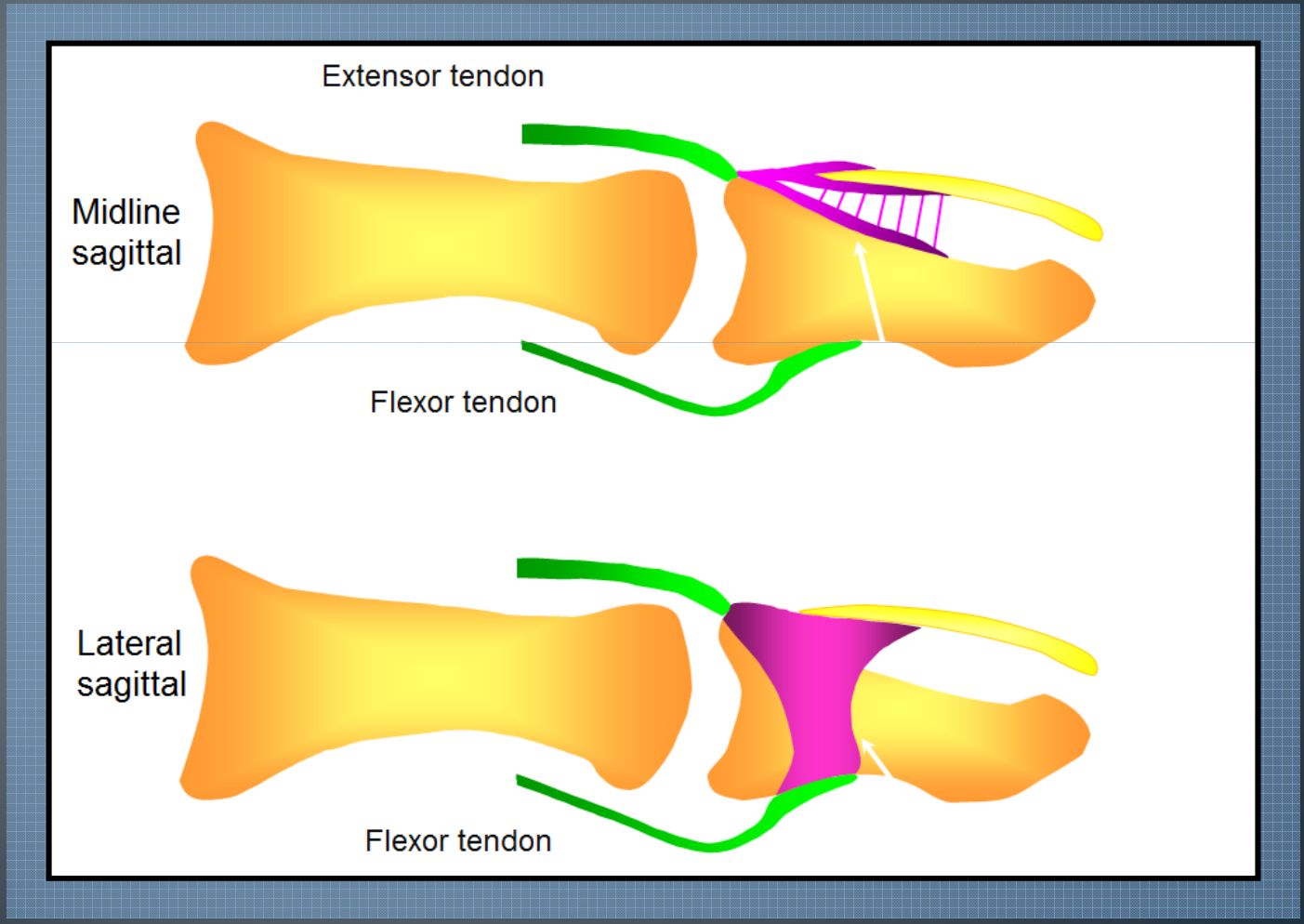
Landells I, et al. Skin Therapy Lett. 2008;13(4):4-7.

Diagnostic workup
Physical examination

- Nails
  - Onycholysis
  - Pitting
  - Hyperkeratosis
  - Oil-drop sign
  - Crumbling
- Signs of joint inflammation
  - Swelling
  - Effusion
  - Synovial thickening
  - Erythema
  - Decreased range of movement
- Other manifestations
  - DIP joint involvement
  - Enthesitis
  - Dactylitis
  - Spondylitis and sacroiliitis
  - Uveitis

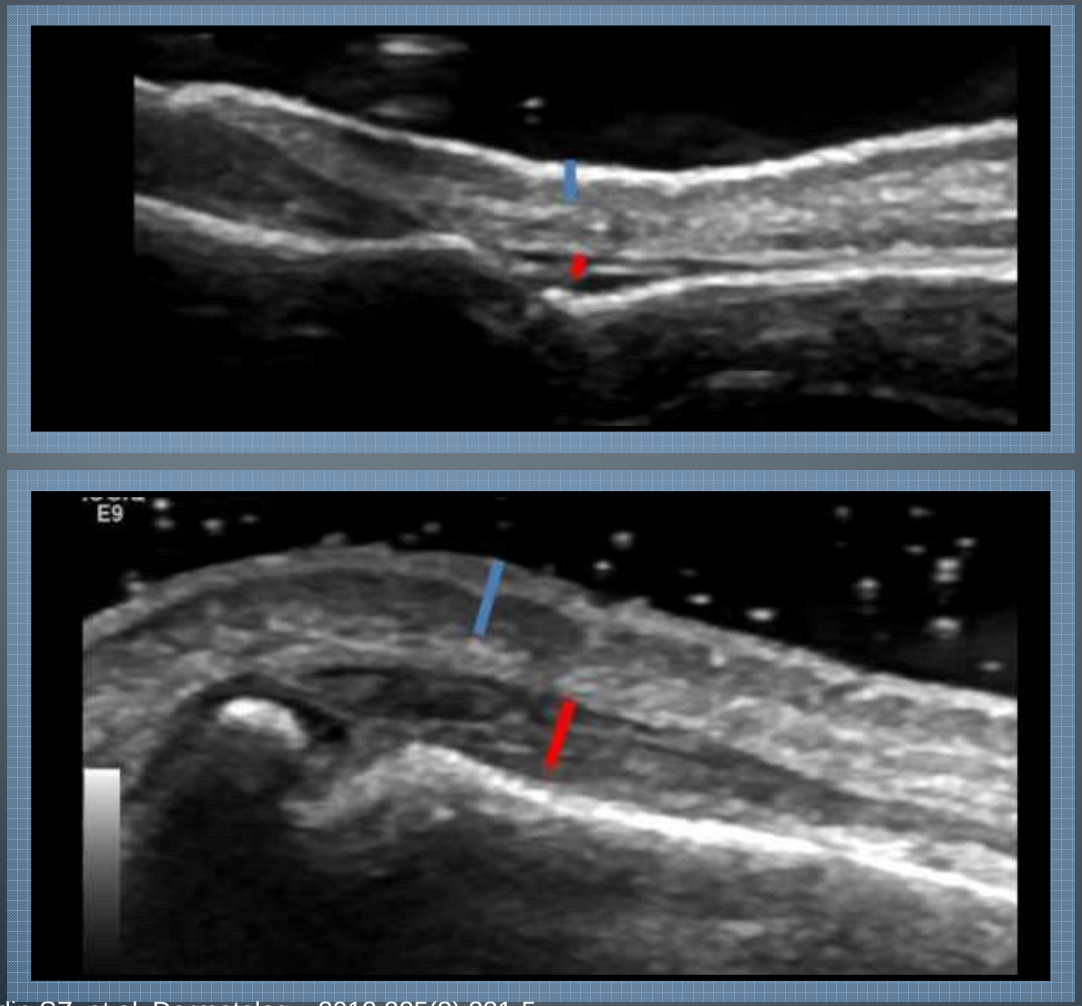
Landells I, et al. Skin Therapy Lett. 2008;13(4):4-7.

The enthesis anchors the nail to the skeleton via Insertions



McGonagle D, et al. Dermatology. 2009;218(2):97-102

DIP extensor enthesopathy in psoriasis

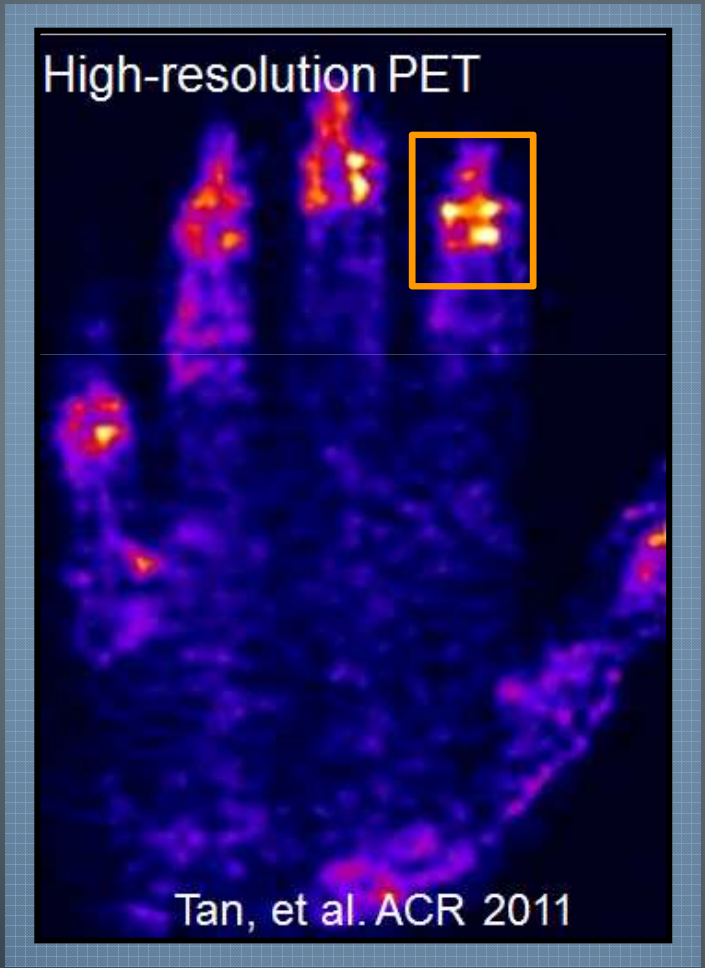


- Normal nail matrix and adjacent extensor tendon enthesis.

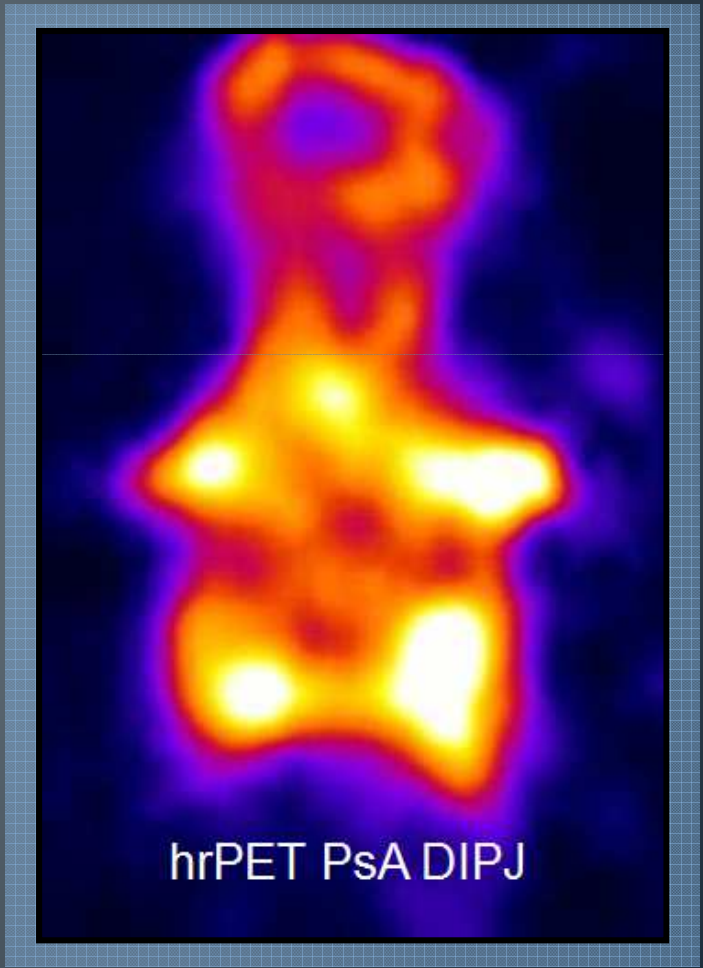
- Extensor tendon enthesopathy is common on high resolution ultrasound in patients with nail disease in both psoriasis and PsA but not patients without disease.

Aydin SZ, et al. Dermatology. 2012;225(3):231-5.

Functional nail-bone integration at enthesis evident on 18F-FDG PET



Courtesy of Professor D McGonagle



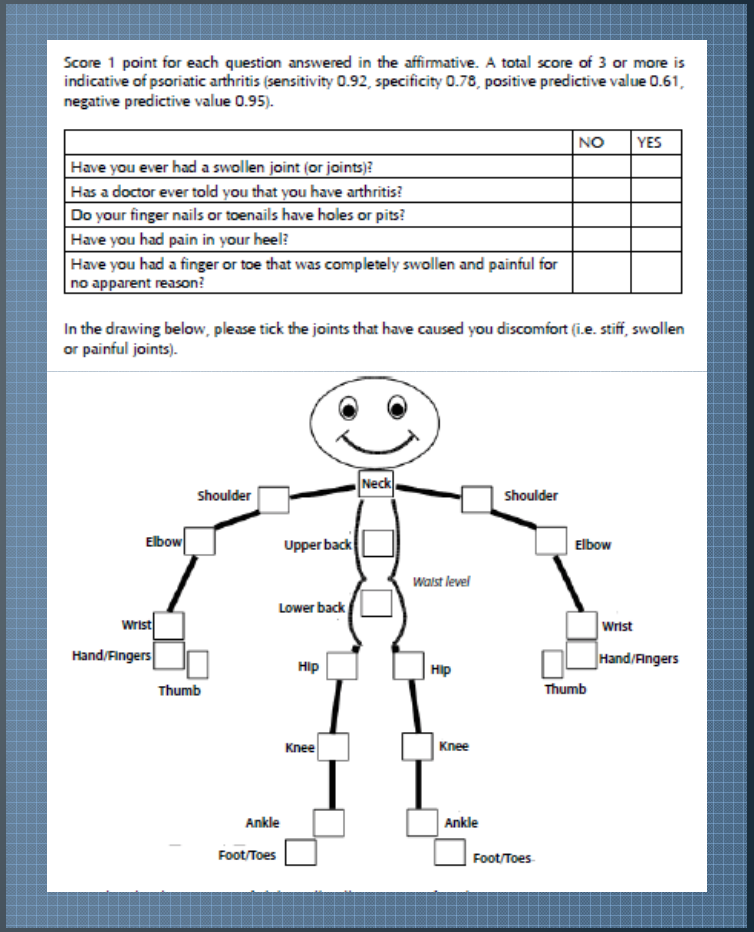
Tan AI, et al. Rheumatology. 2013;52(5):898-904.

1. Ibrahim G, et al. Clin Exp Rheumatol 2009;27(3):469-74; 2. Husni ME, et al. J Am Acad Dermatol 2007;57(4):581-7;
3. Gladman D, et al. Ann Rheum Dis 2008;68(4):497-501; 4. Coates LC, et al. Br J Dermatol. 2013;168(4):802-7.

Diagnostic workup : Screening tools

- **Psoriasis Epidemiology Screening Tool (PEST)[1]**
  - 5-item questionnaire
  - Sensitivity 92%; specificity 78%; positive likelihood ratio 4.1
- **Psoriatic Arthritis Screening and Evaluation Tool (PASE) [2]**
  - 15-item questionnaire
  - Sensitivity 82%; specificity 73%; positive likelihood ratio 3.0.
- **Toronto Psoriatic Arthritis Screen (ToPAS)[3]**
  - 12-item questionnaire
  - Overall sensitivity 86%; specificity 93%; positive likelihood ratio 12.6.
  - Designed for use in psoriasis and non-psoriasis populations

"Although the PEST and ToPAS questionnaires performed slightly better than the PASE questionnaire at identifying PsA, there is little difference between these instruments."[4]



Score 1 point for each question answered in the affirmative. A total score of 3 or more is indicative of psoriatic arthritis (sensitivity 0.92, specificity 0.78, positive predictive value 0.61, negative predictive value 0.95).

	NO	YES
Have you ever had a swollen joint (or joints)?		
Has a doctor ever told you that you have arthritis?		
Do your finger nails or toenails have holes or pits?		
Have you had pain in your heel?		
Have you had a finger or toe that was completely swollen and painful for no apparent reason?		

In the drawing below, please tick the joints that have caused you discomfort (i.e. stiff, swollen or painful joints).

PEST. Courtesy of Professor P Helliwell.[1]

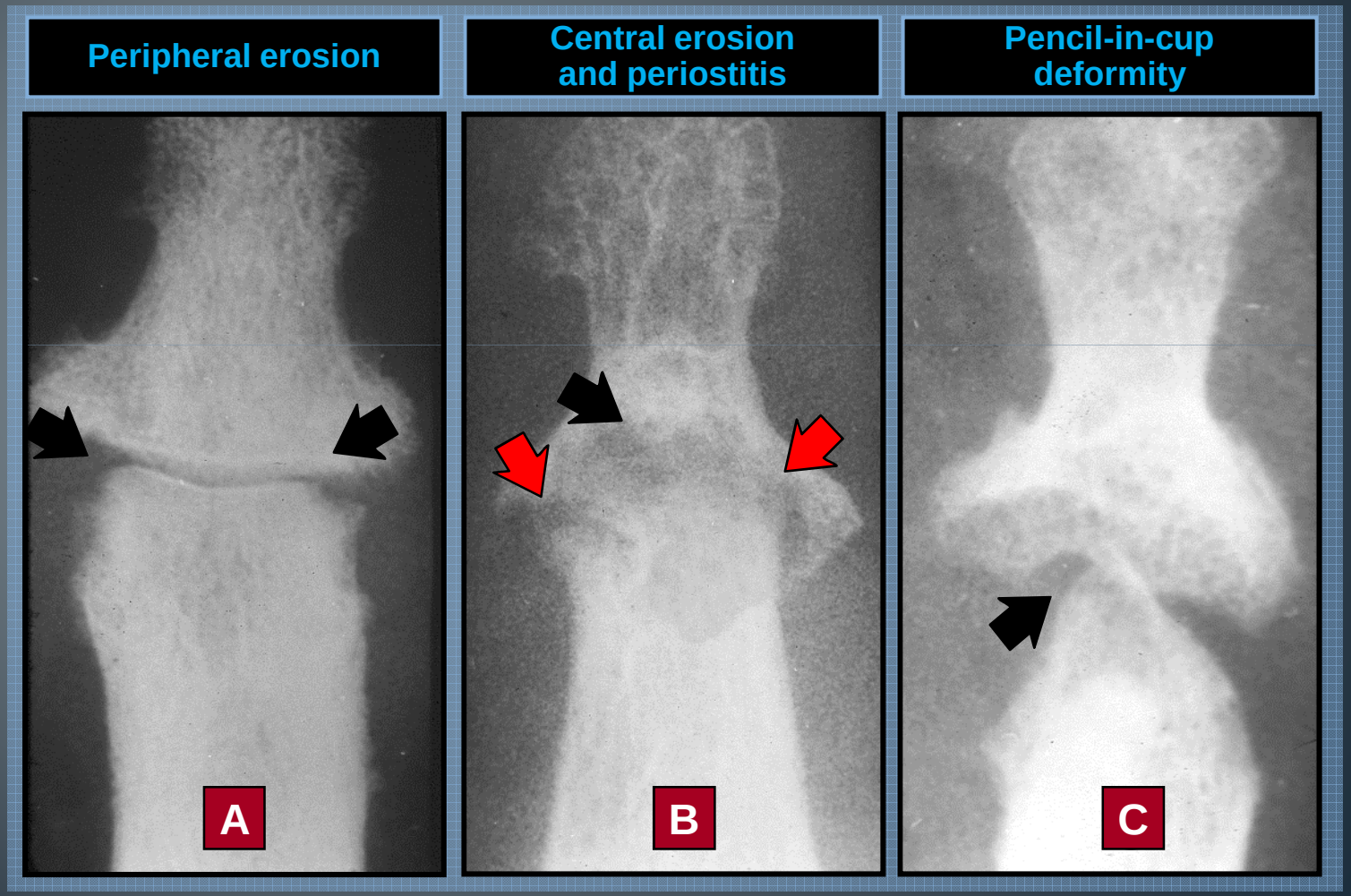
Diagnostic workup

Laboratory tests

- There are no diagnostic laboratory tests for psoriatic arthritis[1]
- However, the following tests should form part of the diagnostic workup[2]
  - Complete blood count
  - Erythrocyte sedimentation rate
  - C-reactive protein
  - Rheumatoid factor
  - Routine renal and hepatic function tests

1. Klinkhoff A. CMAJ. 2000;162(13):1833-8.
2. Landells I, et al. Skin Therapy Lett. 2008;13(4):4-7.

Radiographic Features of PsA

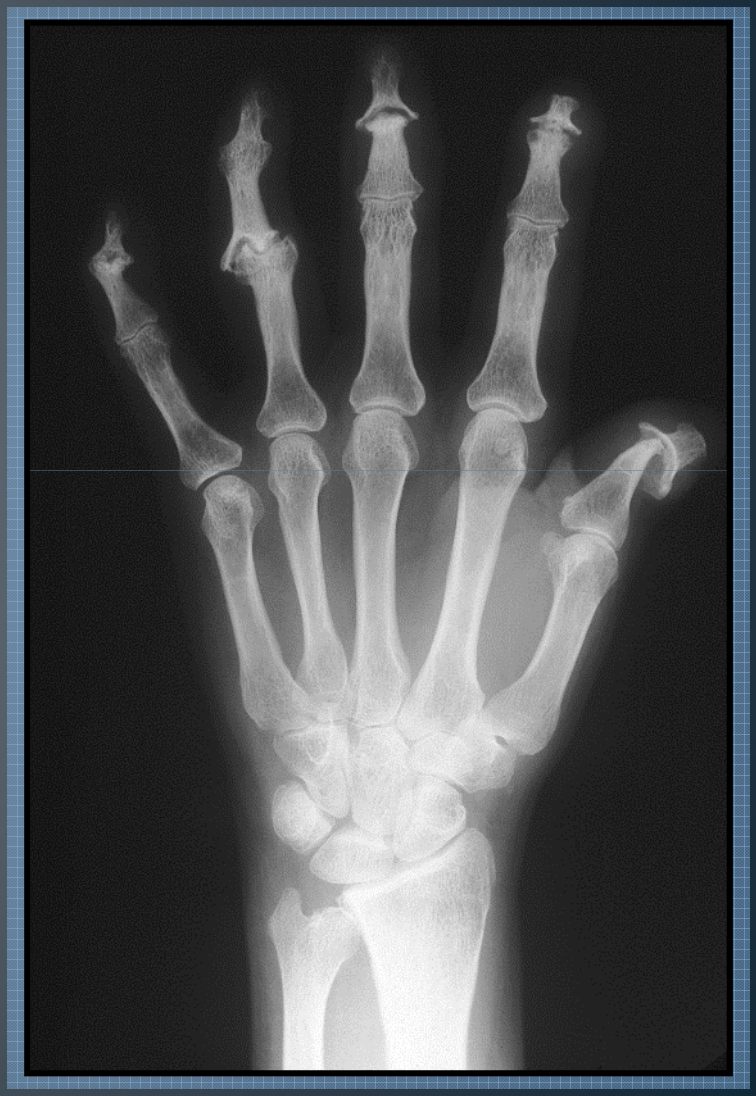


Erosive changes

Proliferative changes

Radiographic Features of PsA

- Up to 57% of patients develop deforming, erosive arthropathy[1,2]
  - Distal tuft resorption, fusion, erosion, malalignment, 'pencil-in-cup deformity', soft-tissue swelling
- Radiographic damage occurs in the early stages of PsA[3]
  - ~30% of patients have erosions at presentation
  - ~50% of patients develop erosions within 3 years of disease onset



1. Torre-Alonso JC, et al. Br J Rheumatol. 1991;30(4):245-50.
2. Gladman DD, et al. Q J Med. 1987;62(238):127-41.
3. Kane D, et al. Rheumatology. 2003;42:1460-8.

Predictores de progresion radiografica en PsA

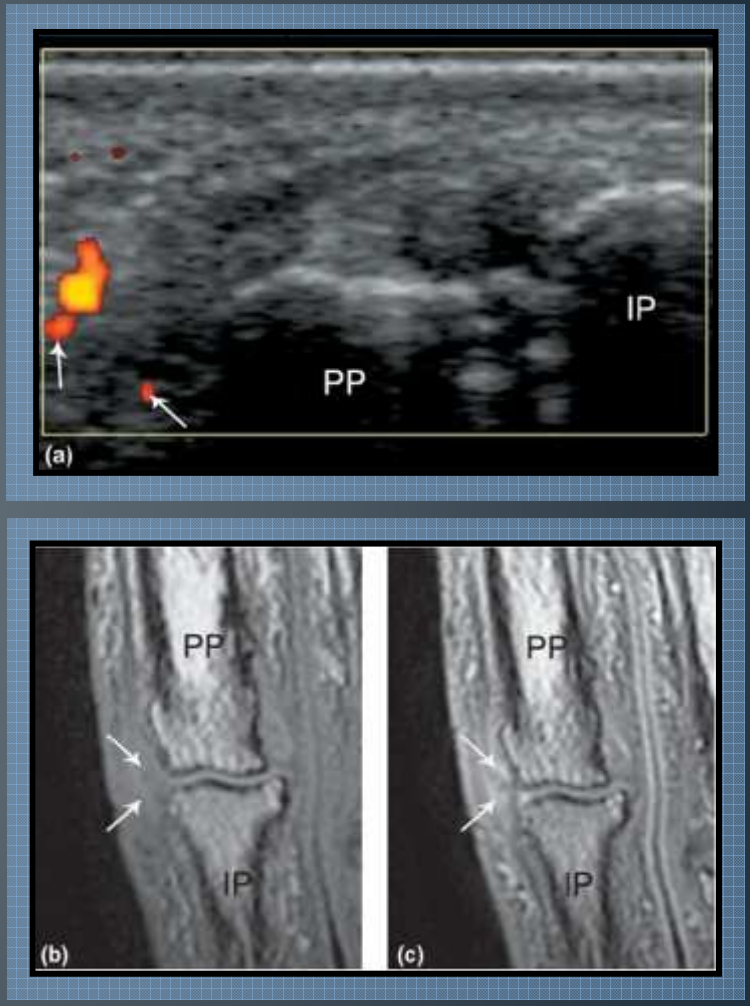
- Elevated baseline CRP[1]
- Poor clinical improvement (skin, joints)[1]
- Prior use of DMARDs[2]
- Baseline MTX use[2]
- Baseline corticosteroid use[2]
- Longer PsA duration (≥1 year)[2]
- Higher HAQ disability score (≥1)[2]
- Higher joint damage[2]

1. Gladman D, et al. Abstract presented at ACR, Nov 6-11 2007, Boston. Abstract 583.
2. Van der Heijde D, et al. Arthritis Rheum. 2007;56(8):2698-707.

Novel imaging techniques

Ultrasonido y RNM

- Ultrasound and MRI are sensitive techniques to depict inflammatory and destructive changes in addition to X-ray and clinical examination
- These modalities have major potential for improved examination of joints, tendons, and entheses in fingers and toes of patients with PsA, but their true value in daily routine has still to be established

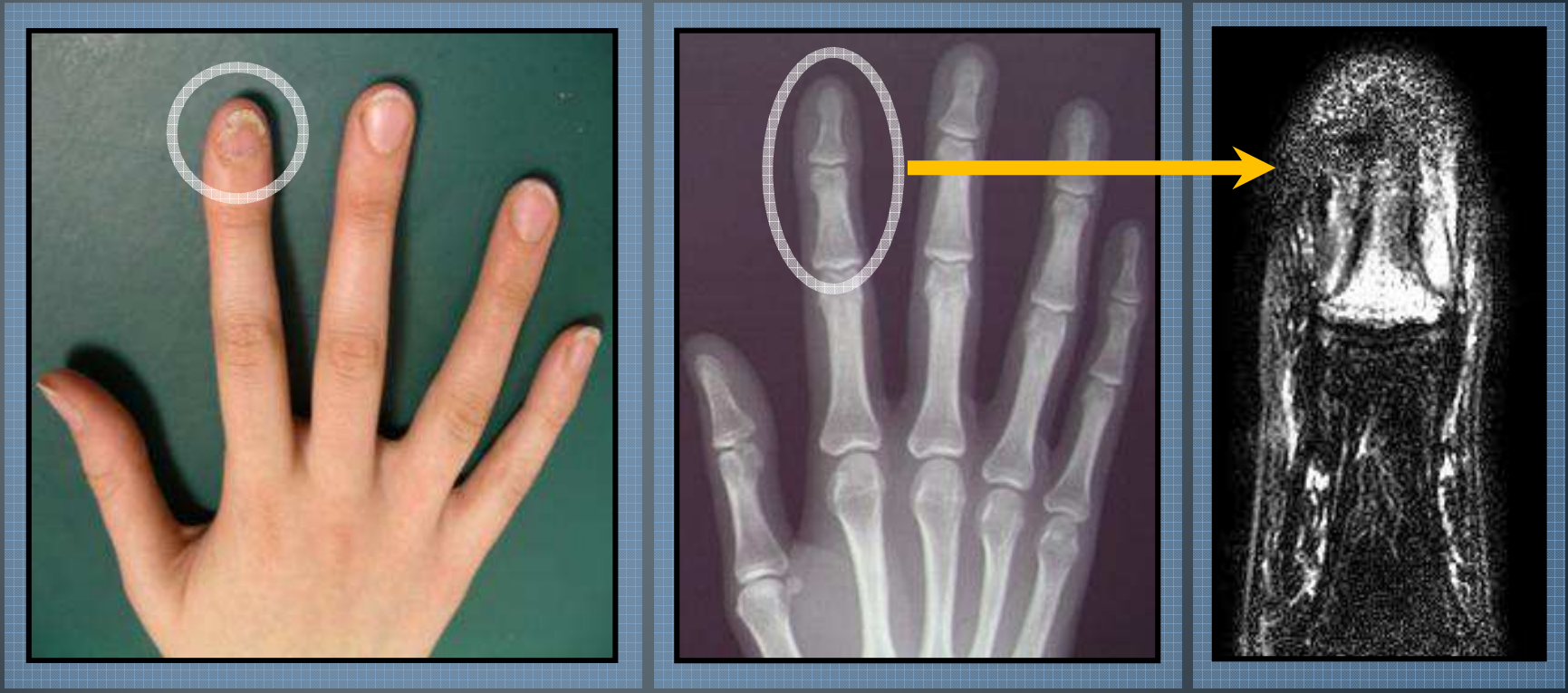


(a) Capsular/extracapsular changes on power Doppler ultrasonography on the radial side of the 2nd proximal interphalangeal joint in a patient with PsA. (b,c) Coronal T1-weighted magnetic resonance images before and after contrast administration showing capsular/extracapsular post-contrast enhancement.

Wiell C, et al. Arthritis Res Ther. 2007;9(6):R119.

Novel imaging techniques

hrMRI facilita el diagnostico de PsA



hrMRI

McGonagle D, et al. Dermatology. 2009;218(2):97-102

ESpondiloartritis y Criterios de Clasificacion

Spondyloarthropathies Axial and Peripheral
AMOR criteria (1990)
ESSG criteria (1991)

Axial Spondyloarthritis
ASAS classification 2009

Peripheral Spondyloarthritis
ASAS classification 2010

Ankylosing spondylitis
Prototype of axial spondylitidis
Modified New York criteria 1984

(IFX) ,ETN, ADA, CZP, GLM,ABA indications

Psoriatic arthritis
From Moll and Wright 1973 to CASPAR criteria 2006

ESSG: European Spondyloarthropathy Study Group; ASAS: Assessment of Spondyloarthritis International Society; CASPAR: Classification Criteria for Psoriatic Arthritis

Sieper J, Rudwaleit M, Baraliakos X , et al. Ann Rheum Dis 2009;68:ii1-ii44;
Taylor W, Gladman D, Helliwell P, et al. Arthritis & Rheum 2006;54: 2665-73
van der Heijde, Sieper J, Maksymowych WP, et al. Ann Rheum Dis 2011;70:905-8

PsA : Eligiendo Terapia

- Eficacia en artritis, entesitis, dactilitis, espondilitis
- Eficacia en psoriasis, uñas, y otras manifestaciones extra-articulares
- Perfil de seguridad
- Metodos de administración
- Consideraciones sobre la calidad de vida
- Realidades económicas

PsA: Quienes son los progresores?

- Elementos a considerar:
  1. **Falta de respuesta a AINEs**
  2. **Numero de articulaciones involucradas**
  3. **Erosiones a los RX**
  4. **ESR y PCR elevadas**
  5. **Discapacidad**
  6. **Duracion de la enfermedad(<2 años)**

  - **Mortalidad elevada relativa respecto a poblacion general.**

Psoriatic Arthritis Assessment Tools

GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

Joints[1]

TJC (tender joint count)
SJC (swollen joint count)

Enthesitis/Dactylitis[1]

LDI (Leeds dactylitis index)
LEI (Leeds enthesitis index)
MEI (Mander/Newcastle enthesitis index)
MASES (Maastricht AS enthesitis score)
SPARCC (SpA research consortium of Canada)

Skin/Nails[1]

BSA (body surface area)
PASI (disease area and severity index)
PSGA/PGA (physician static global assessment)
NAPSI (nail psoriasis severity index) / **MNAPSI** (modified nail psoriasis severity index)
Nail VAS

Function/Quality of life[1]

HAQ-DI (health assessment questionnaire disability index)
DLQI (dermatology life quality index)
EQ-5D (EuroQoL 5 domain)
PsAQOL (PsA quality of life)
PsAID (PsA Impact of Disease)[3]
SF-36 (short form 36)

Composite Measures

PsARC[1] (PsA response criteria)
PSAJAI[1] (PsA joint activity index)
DAPSA[1] (disease activity in PsA)
CPDAI[1] (composite psoriatic disease activity index)
MDA*[1] (minimal disease activity)
PASDAS*[2] (PsA disease activity score)
AMDF[2] (Arithmetic mean of desirability functions)

*Includes joint, enthesitis and/or dactylitis, skin and function and/or quality of life assessments

1. Mease PJ. Arthritis Care Res 2011;63(suppl 11):S64-85;
2. Helliwell PS et al. Ann Rheum Dis 2013;72:986-991
3. Gossec L et al. Ann Rheum Dis 2014;73:1012-9

Tratamientos basados en evidencias para los dominios clinicos de PsA

	Artritis periferica	Enfermedades de piel y uñas	**Enfermedad axial**	Dactilitis	entesitis
AINES	X		X		
Esteroides extra.articulares	X				
Topicas		X			
Fisioterapia			X		
Psoralenos UVA UVB		X			
DMARDs(MTX,CsA, SSZ, Lef)	X	X			
Biologicos (anti TNF))	X	X	X	X	X

EULAR Recommendations for Management of PsA

eular

Recommendation 2 - DMARDs

Drug	/ N patients	studies	
Methotrexate	3 / 93	7	Efficacy on joints and skin X-rays: no data
Sulfasalazine	7 / 666	2	Efficacy on joints Skin no efficacy X-rays: no data
Leflunomide	1 / 190	3	Efficacy on joints Skin limited efficacy X-rays: no data
Cyclosporin	3 / 206	6	Efficacy on joints and skin X-rays: no data

Other drugs assessed: hydroxychloroquine, Gold/Auranofin, Azathioprin, D-penicillamine, Fumaric Acid, Retinoids, Colchicine

Gossec L, et al. Ann Rheum Dis 2012;71:4-12

EULAR Recommendations for Management of PsA

Recommendation 5

In patients with active arthritis and an inadequate response to at least **one** synthetic disease-modifying anti-rheumatic drug, such as methotrexate, therapy with a tumour necrosis factor inhibitor should be commenced.

1b	B
8.9±1.6	

- Efficacy of TNF blockers on joints, skin and radiographic damage
- Prescription after one DMARD: expert opinion

Gossec L, et al. Ann Rheum Dis 2012;71:4-12

TNF blockers are efficacious on joints (PsARC)

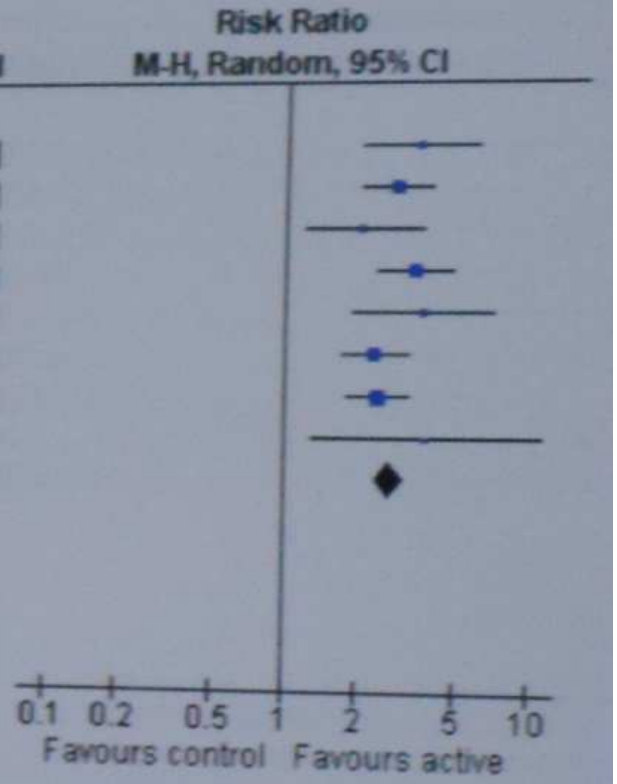
Risk ratio for PsARC response at 12 weeks versus placebo

RR 2.7 [2.4, 3.2]

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.22.1 anti-TNF						
Antoni 2005 INF (IMPACT)	39	52	11	52	6.9%	3.55 [2.05, 6.13]
Antoni 2005 INF (IMPACT2) (1)	77	100	27	100	18.0%	2.85 [2.03, 4.01]
Genovese 2007 ADA	26	51	12	49	6.6%	2.08 [1.19, 3.65]
Kavanaugh 2008 GOL (2)	212	292	24	113	15.8%	3.42 [2.38, 4.91]
Mease 2000 ETAN	26	30	7	30	4.7%	3.71 [1.91, 7.21]
Mease 2004 ETAN	73	101	32	104	21.2%	2.35 [1.72, 3.21]
Mease 2005 ADA	94	151	42	162	24.9%	2.40 [1.80, 3.20]
Vander Cruyssen 2007 INF	9	9	2	9	1.8%	3.80 [1.29, 11.22]
Subtotal (95% CI)		**786**		**619**	**100.0%**	**2.73 [2.36, 3.15]**
Total events	556		157			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.29$, $df = 7$ ($P = 0.51$); $I^2 = 0\%$

Test for overall effect: $Z = 13.67$ ($P < 0.00001$)



(1) 14 weeks

(2) 14 weeks

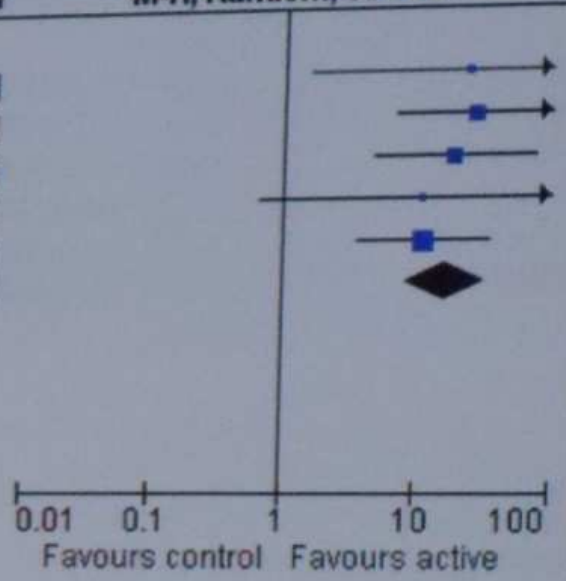
Ash Z, et al. Ann Rheum Dis 2012;71:319-26

TNF blockers are efficacious on skin (PASI 75)

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.31.1 anti-TNF						
Antoni 2005 INF (IMPACT) (1)	15	22	0	17	6.3%	24.26 [1.55, 378.66]
Antoni 2005 INF (IMPACT2) (2)	53	83	2	87	25.1%	27.78 [6.99, 110.35]
Kavanaugh 2008 GOL (3)	106	217	2	79	25.3%	19.29 [4.88, 76.31]
Mease 2000 ETAN	5	19	0	19	6.0%	11.00 [0.65, 186.02]
Mease 2005 ADA	34	69	3	69	37.3%	11.33 [3.65, 35.17]
Subtotal (95% CI)		**410**		**271**	**100.0%**	**17.01 [8.52, 33.96]**
Total events	213		7			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.21$, df = 4 (P = 0.88); $I^2 = 0\%$

Test for overall effect: Z = 8.03 (P < 0.00001)



(1) 16 weeks
(2) 14 weeks
(3) 14 weeks

Risk ratio for PASI 75 response at 12 weeks versus placebo

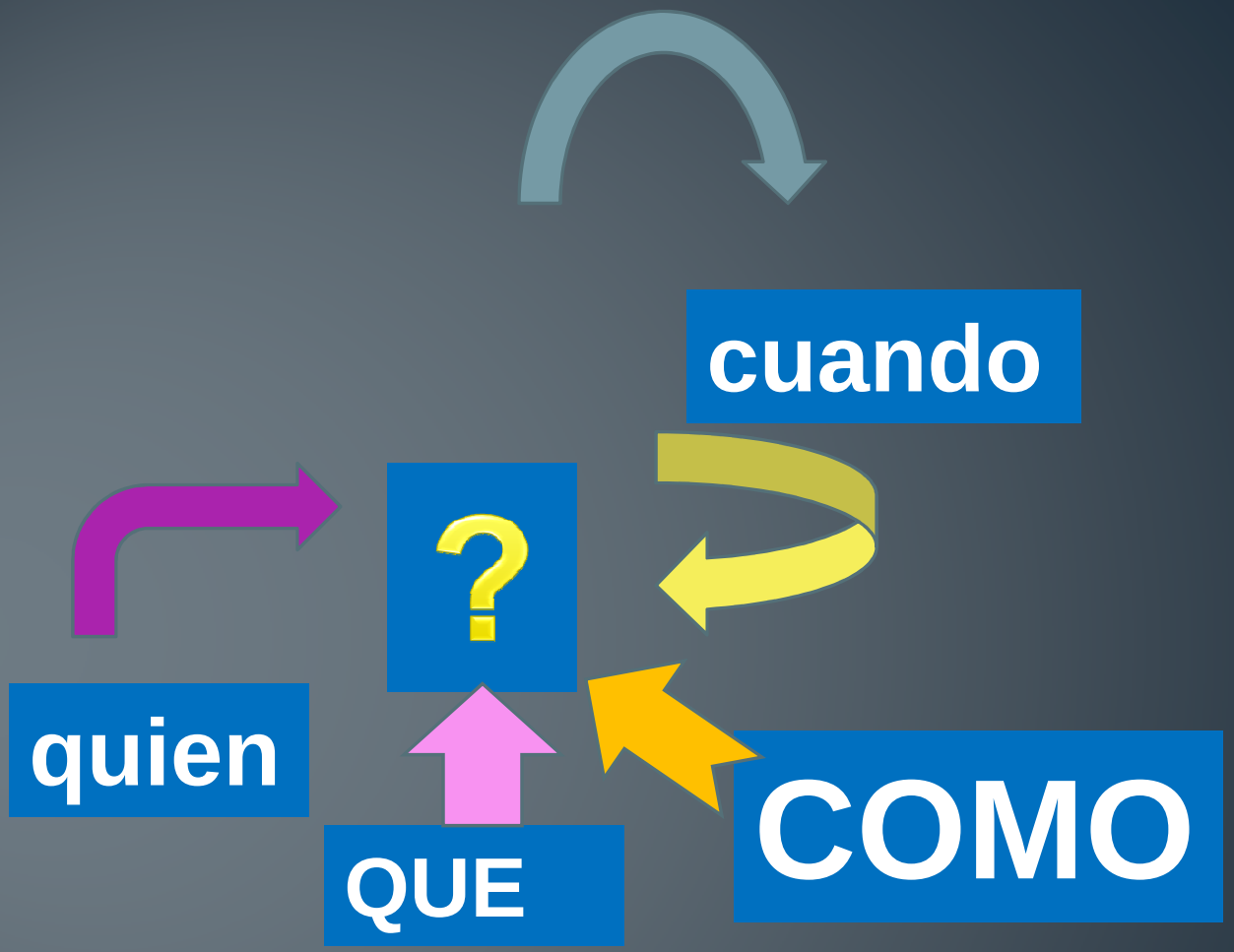
RR 17.0 [8.5, 33.9]

Ash Z, et al. Ann Rheum Dis 2012;71:319-26

Anti-TNF in PsA Outcomes

- **Psoriasis**
  - PASI 75 response ~60% with most agents
- **Enthesitis**
  - ~60-75% improvement
  - Assessment methods: 4-point, MASES, Leeds, SPARCC
- **Dactylitis**
  - ~60% improvement
  - Assessment methods: Count, score, Leeds dactylometer
- **Function**
  - Significant improvement achieved as assessed by HAQ
- **QOL**
  - Significant improvements in SF-36, PsAQOL, DLQI, EQ-5D

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


cuando
?
quien
QUE
COMO

- **Remission**
  Low Disease Activity

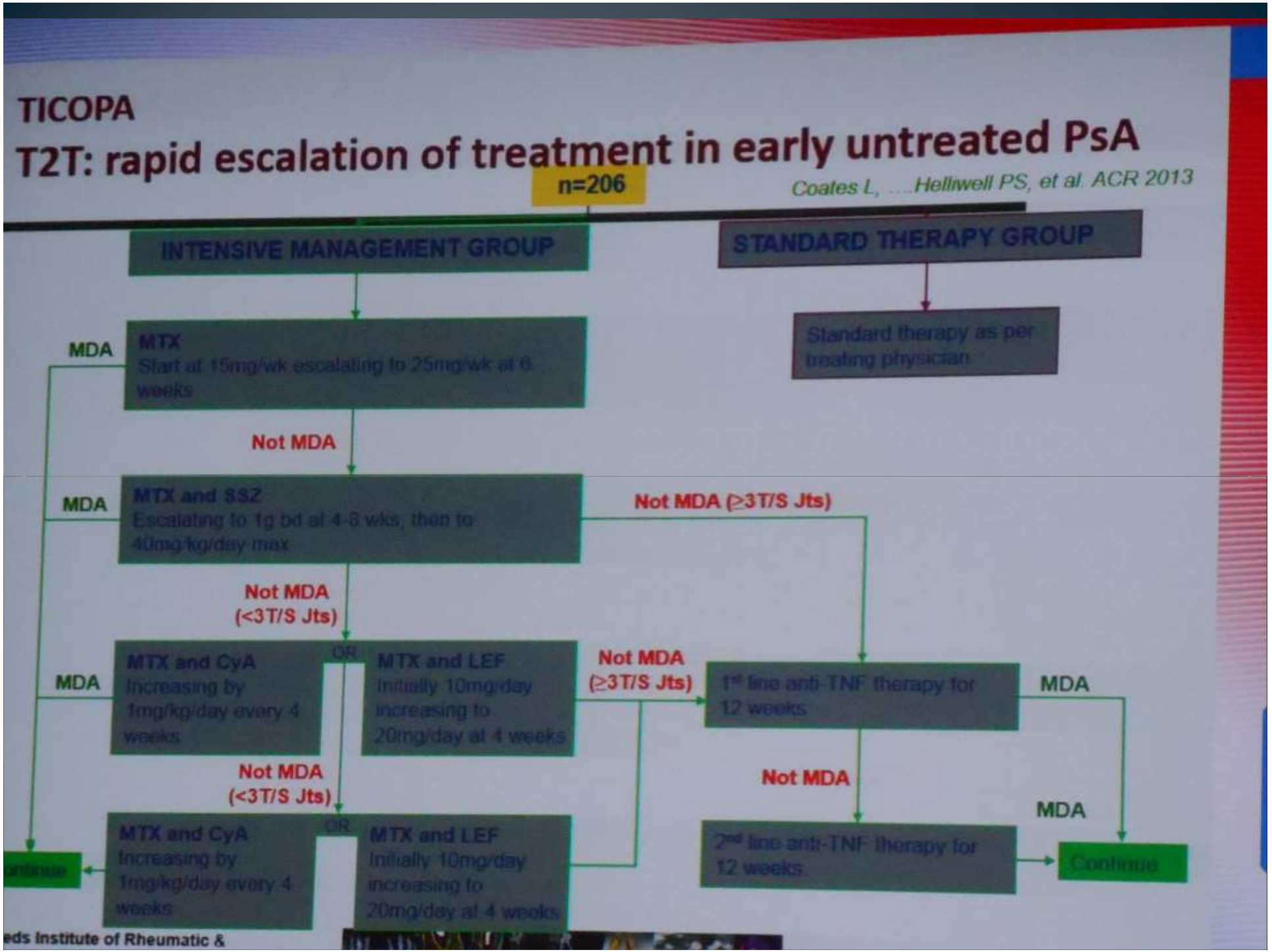
Current Treat-to-Target recommendations

Smolen J, et al. Ann Rheum Dis 2013, (june E-pub)

Minimal Disease Activity Criteria (MDA) (GRAPPA consensus)

- A patient is classified as in MDA when meeting 5 of 7 of the following criteria:
  - tender joint count ≤1
  - swollen joint count ≤1
  - PASI ≤1 or BSA ≤3
  - patient pain VAS ≤15
  - patient global activity VAS ≤20
  - HAQ ≤0.5
  - tender entheseal points ≤1

Coates L; et al. Ann Rheum Dis. 2010;69(1):48-53


TICOPA
T2T: rapid escalation of treatment in early untreated PsA
n=206
Coates L, ….Helliwell PS, et al. ACR 2013
INTENSIVE MANAGEMENT GROUP
STANDARD THERAPY GROUP
MTX
Start at 15mg/wk escalating to 25mg/wk at 6 weeks
Standard therapy as per treating physician
MDA
Not MDA
MTX and SSZ
Escalating to 1g bd at 4-8 wks, then to 40mg/kg/day max
MDA
Not MDA (≥3T/S Jts)
Not MDA (<3T/S Jts)
MTX and CyA
Increasing by 1mg/kg/day every 4 weeks
OR
MTX and LEF
Initially 10mg/day increasing to 20mg/day at 4 weeks
MDA
Not MDA (≥3T/S Jts)
1st line anti-TNF therapy for 12 weeks
MDA
Not MDA (<3T/S Jts)
MTX and CyA
Increasing by 1mg/kg/day every 4 weeks
OR
MTX and LEF
Initially 10mg/day increasing to 20mg/day at 4 weeks
Not MDA
2nd line anti-TNF therapy for 12 weeks
MDA
Continue
eds Institute of Rheumatic &

ULAR Recommendations for PsA

Recommendation 9

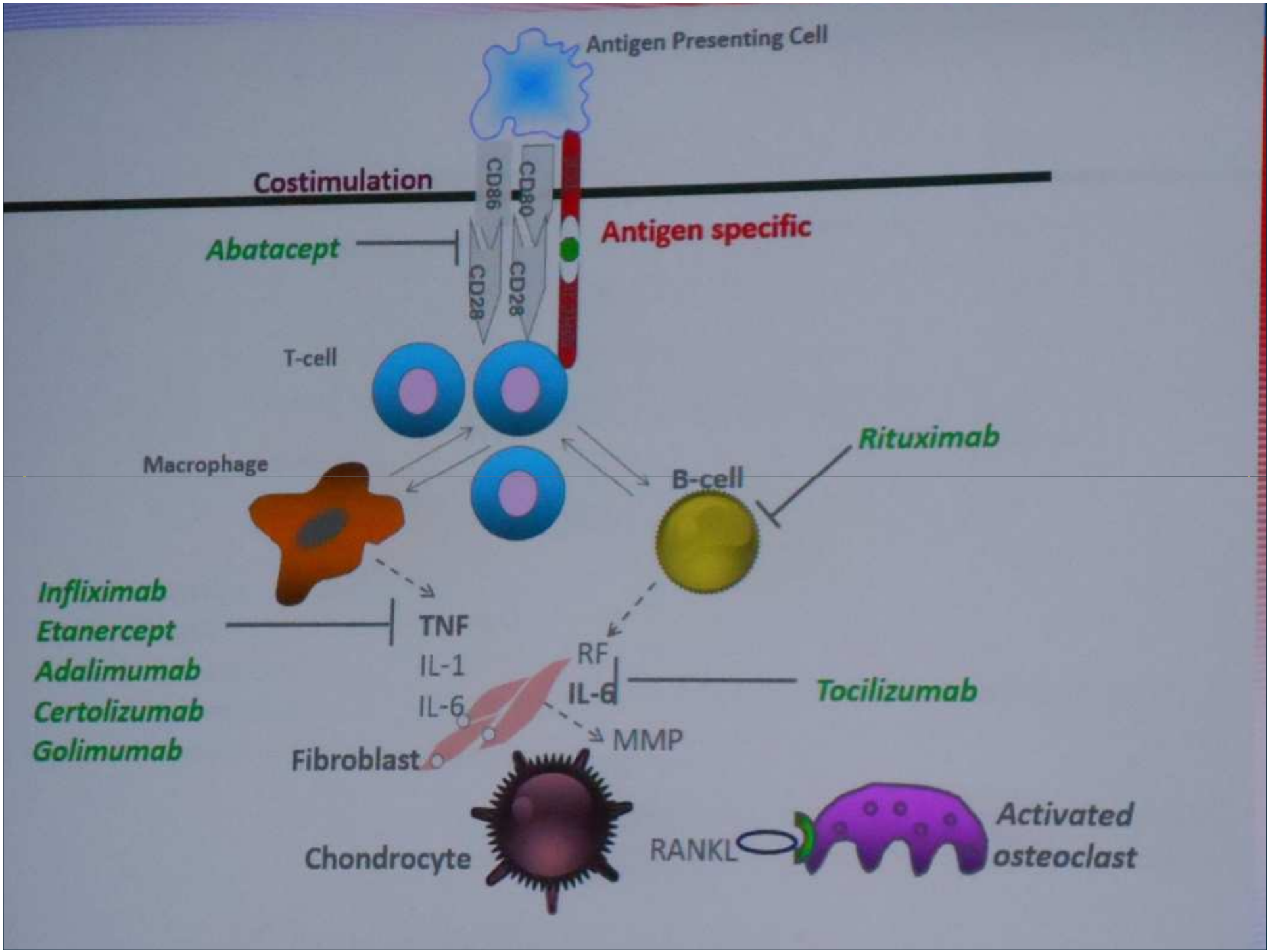
eular

In patients who fail to respond adequately to one anti-TNF agent, switching to another anti-TNF agent should be considered.

2b	B
8.7±2.1	

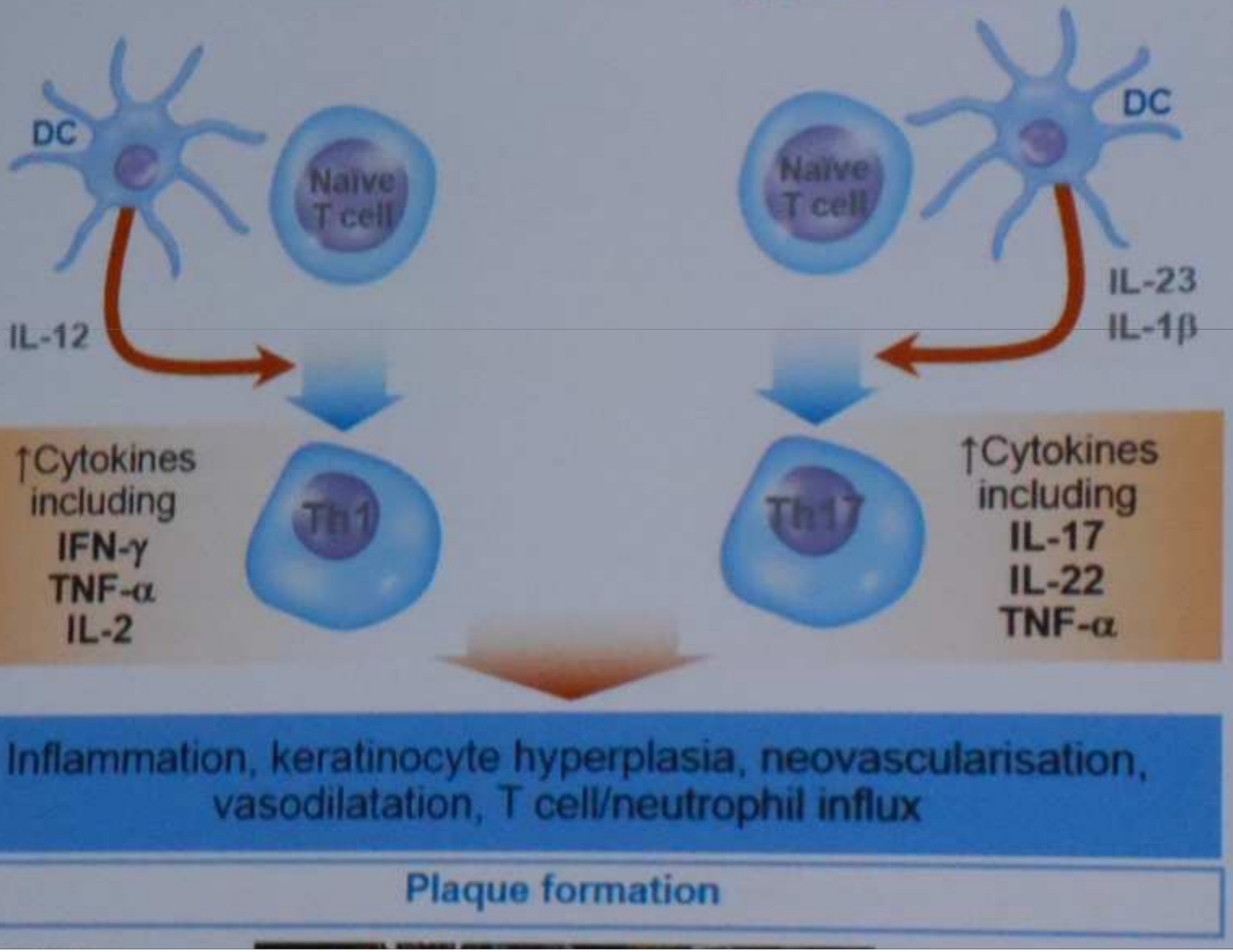
- Some data on efficacy of switching

Gossec L, et al. Ann Rheum Dis 2012;71:4-12

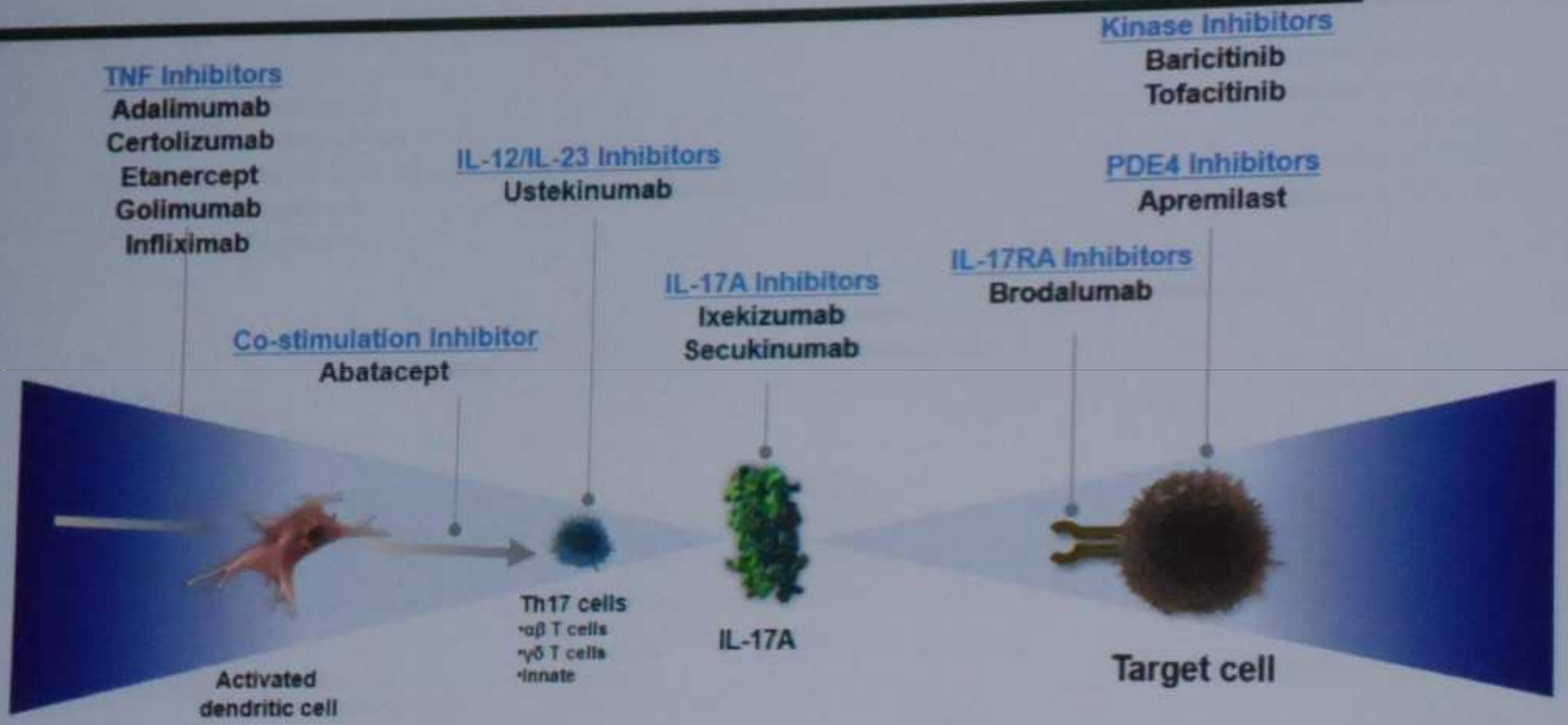

Antigen Presenting Cell
Costimulation
CD86
CD80
CD28
CD28
Antigen specific
Abatacept
T-cell
Macrophage
B-cell
Rituximab
Infliximab
Etanercept
Adalimumab
Certolizumab
Golimumab
TNF
IL-1
IL-6
RF
IL-6
Tocilizumab
MMP
Fibroblast
Chondrocyte
RANKL
Activated
osteoclast

Genetic studies in SpA (Pso) point towards the IL-12 and IL-23 axis

Nestle FO, et al. J Invest Dermatol. 2004;123



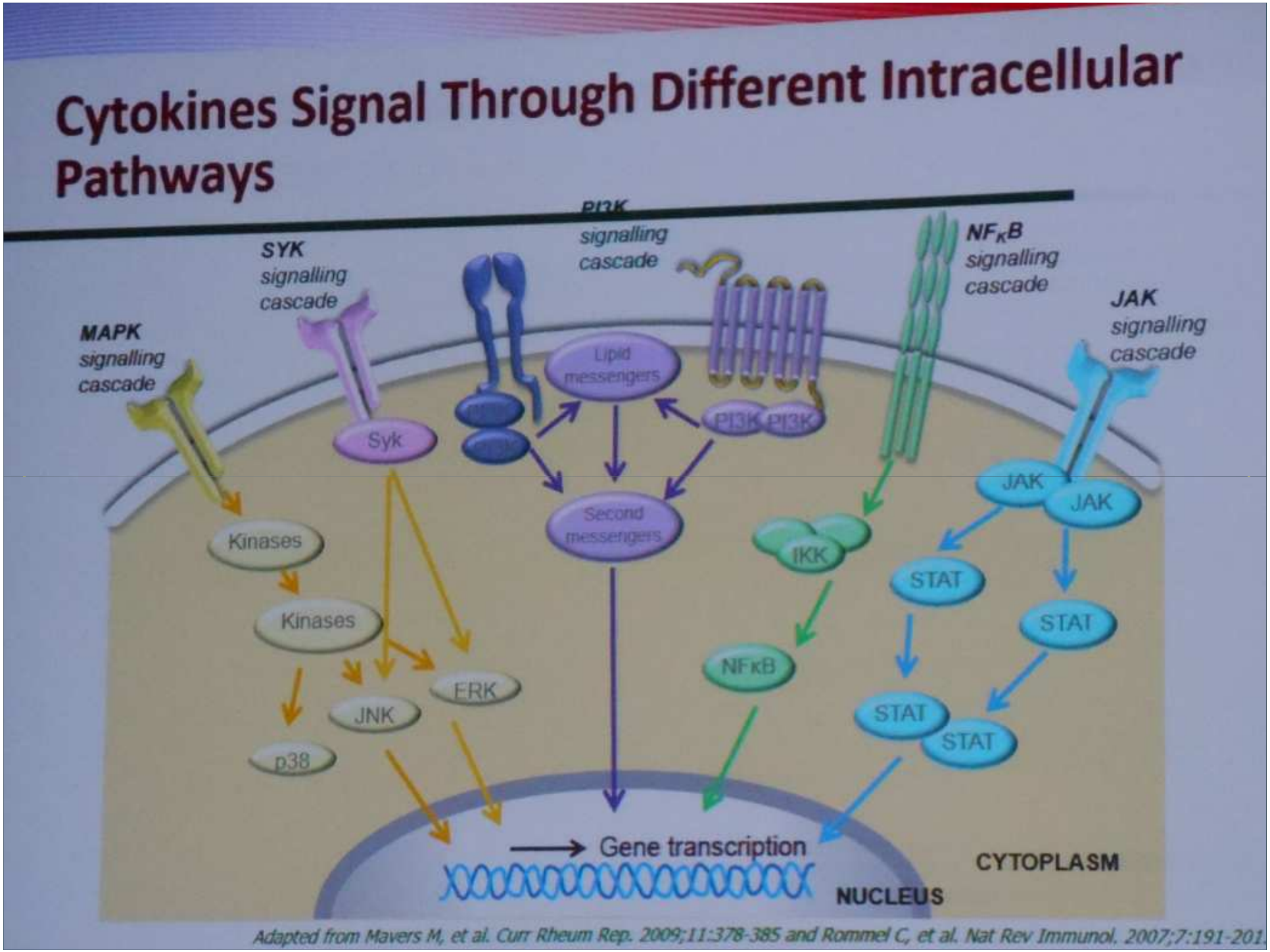
IL-17A Pathway Inhibitors:
Different Mechanisms of Action



PDE4, phosphodiesterase type 4; Th17, T helper 17 cell.

Adapted from Nestle F 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.

Cytokines Signal Through Different Intracellular Pathways

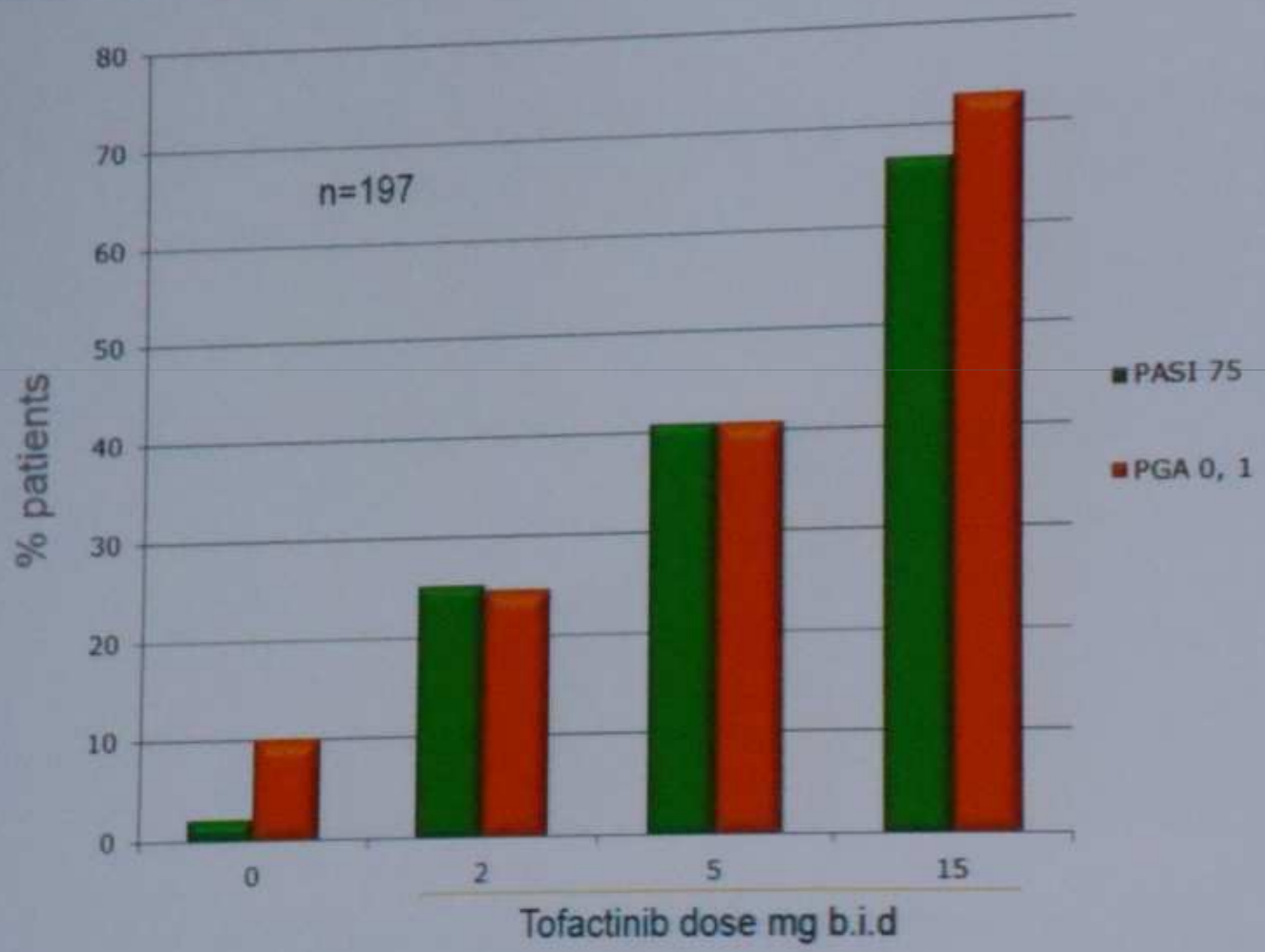


Adapted from Mavers M, et al. Curr Rheum Rep. 2009;11:378-385 and Rommel C, et al. Nat Rev Immunol. 2007;7:191-201.

Ventajas Posibles

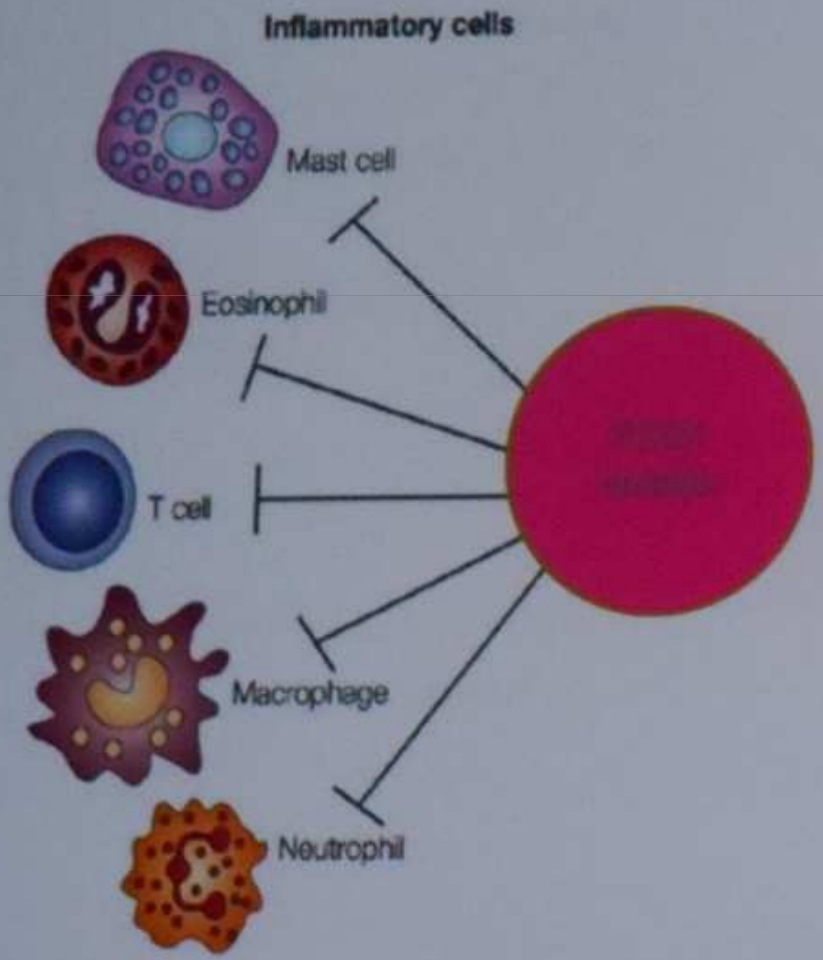
- Pequeño peso molecular
- Comparten accion biologica potente al dirigirse al blanco celular de estructuras y proteinas de señalizacion intracelular
- Tienen un tiempo de manufactura menor que las drogas biologicas
- Son oralmente biodosponibles
- Mas costo-efectivo

JAK inhibitors
Tofacitinib (CP-690550) Phase 2b data in PsO



Harness J, et al. Poster presented at AAD. New Orleans Feb 3-8 2011. P3318
Papp KA, et al. Br J Dermatol 2012;167:668-77

PDE4 inhibitors: Apremilast/CC-10004

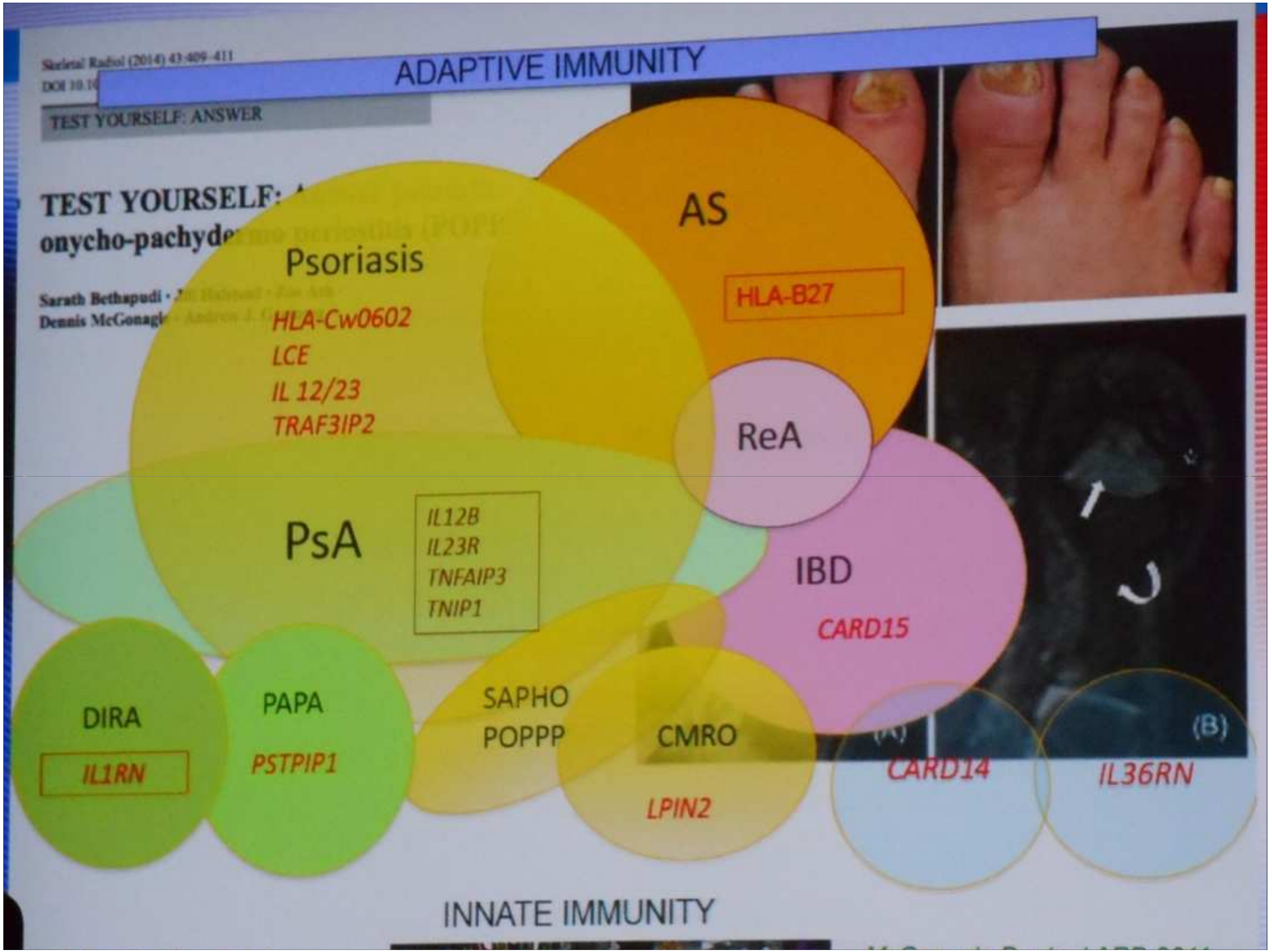


- Type 4 phosphodiesterases (PDE4) play an important role in immune cells through hydrolysis of cAMP
- PDE4 inhibition suppresses immune and inflammatory responses
- PDE4 is thus a valid therapeutic target for immune-mediated pathologies

McCann FE, et al. Arthritis Res Ther. 2010; 12(3): R107.

Summary of efficacy data for new targeted treatments in SpA

		axSpA/ AS	PsA	Psoriasis	Crohn's
B cells	Rituximab	-	-	NA	NA
T cells	Abatacept	–	+	+	NA
IL-6	Tocilizumab	–	NA	NA	±
IL-17	Secukinumab	+	+	+	-
IL-12/23	Ustekinumab	++	±	+	+
PDE-4	Apremilast	+	+	+	NA


ADAPTIVE IMMUNITY
Skeletal Radiol (2014) 43:409–411
TEST YOURSELF: ANSWER
TEST YOURSELF:
onycho-pachyde
Sarath Bethapudi
Dennis McGonagle
Psoriasis
HLA-Cw0602
LCE
IL 12/23
TRAF3IP2
AS
HLA-B27
ReA
PsA
IL12B
IL23R
TNFAIP3
TNIP1
IBD
CARD15
DIRA
IL1RN
PAPA
PSTPIP1
SAPHO
POPPP
CMRO
LPIN2
CARD14
IL36RN
(A)
(B)
INNATE IMMUNITY

Espondiloartropatias: Una talla no sirve para todos!