Spondyl(o)arthropathies - classification and management

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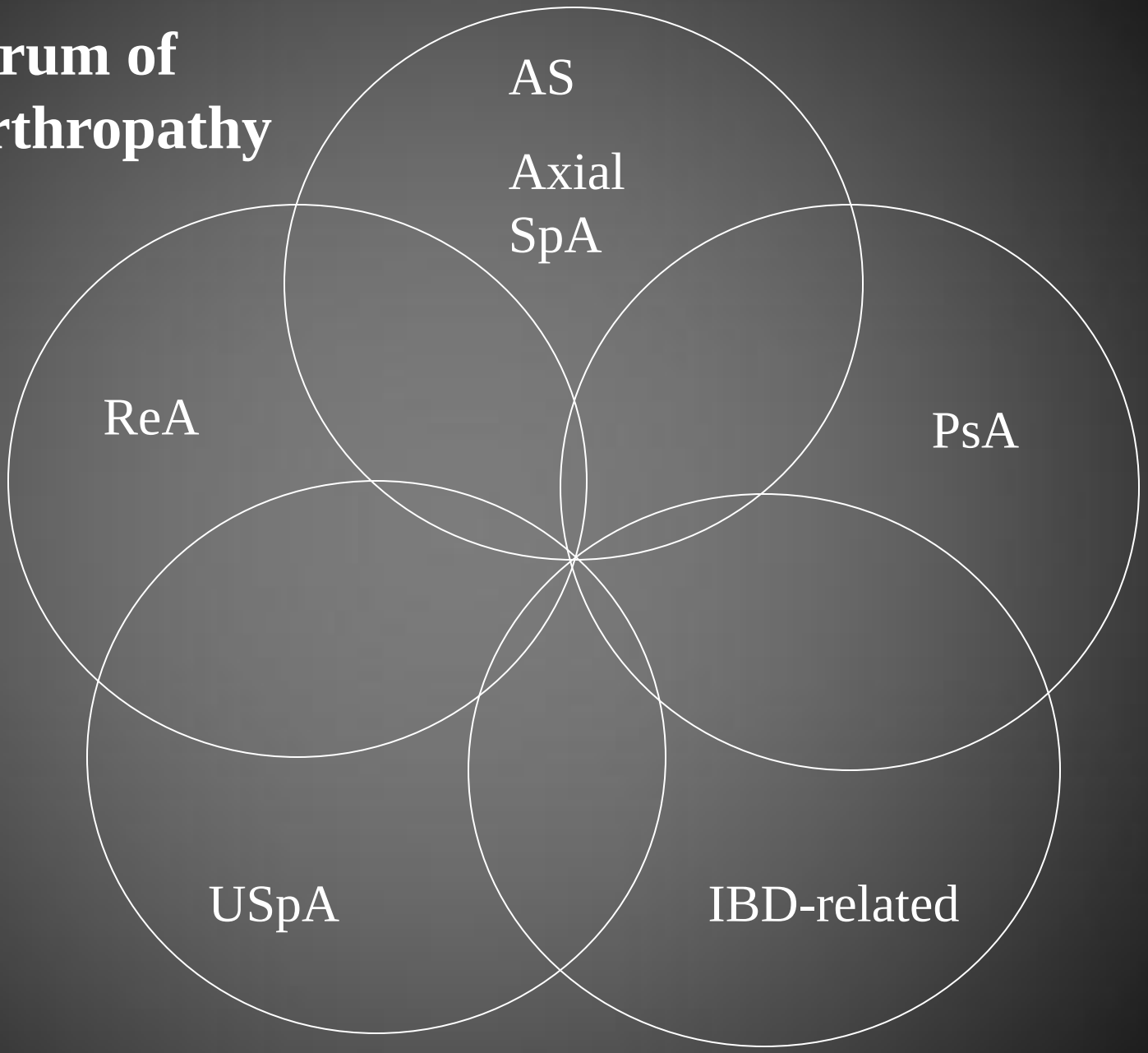
Cambridge
2014

Spondylarthropathies

- Ankylosing spondylitis
- Axial SpA
- Psoriatic arthritis
- Reactive arthritis
- IBD-related. Enteropathic SpA (e.g. Crohn's)
- Juvenile SpA
- *Seronegative enthesopathic/arthropathy syndrome*
- ?Enthesitis-related Arthritis (children)
- Undifferentiated spondylarthritis (USpA)

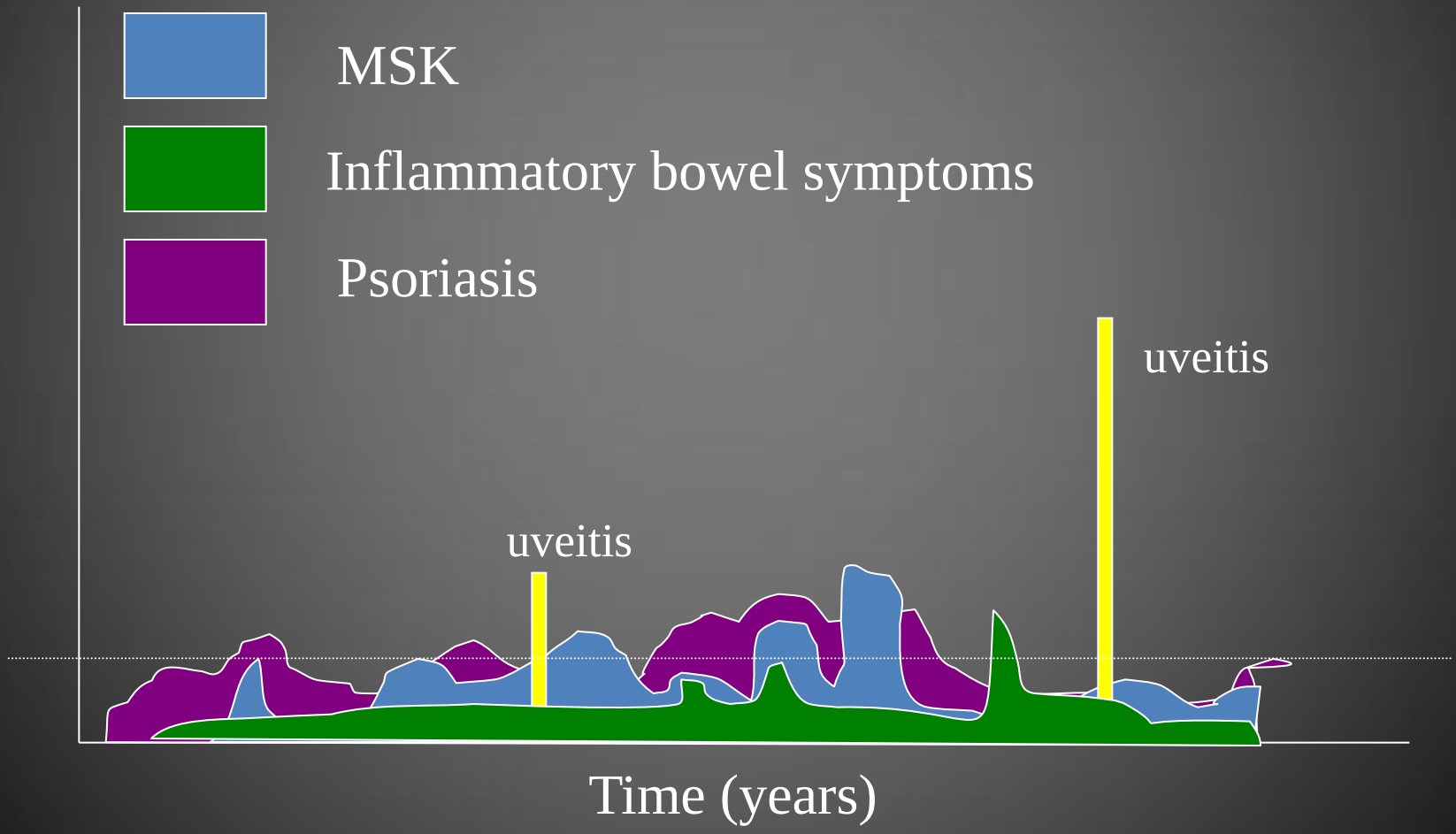
The spectrum of spondylarthropathy



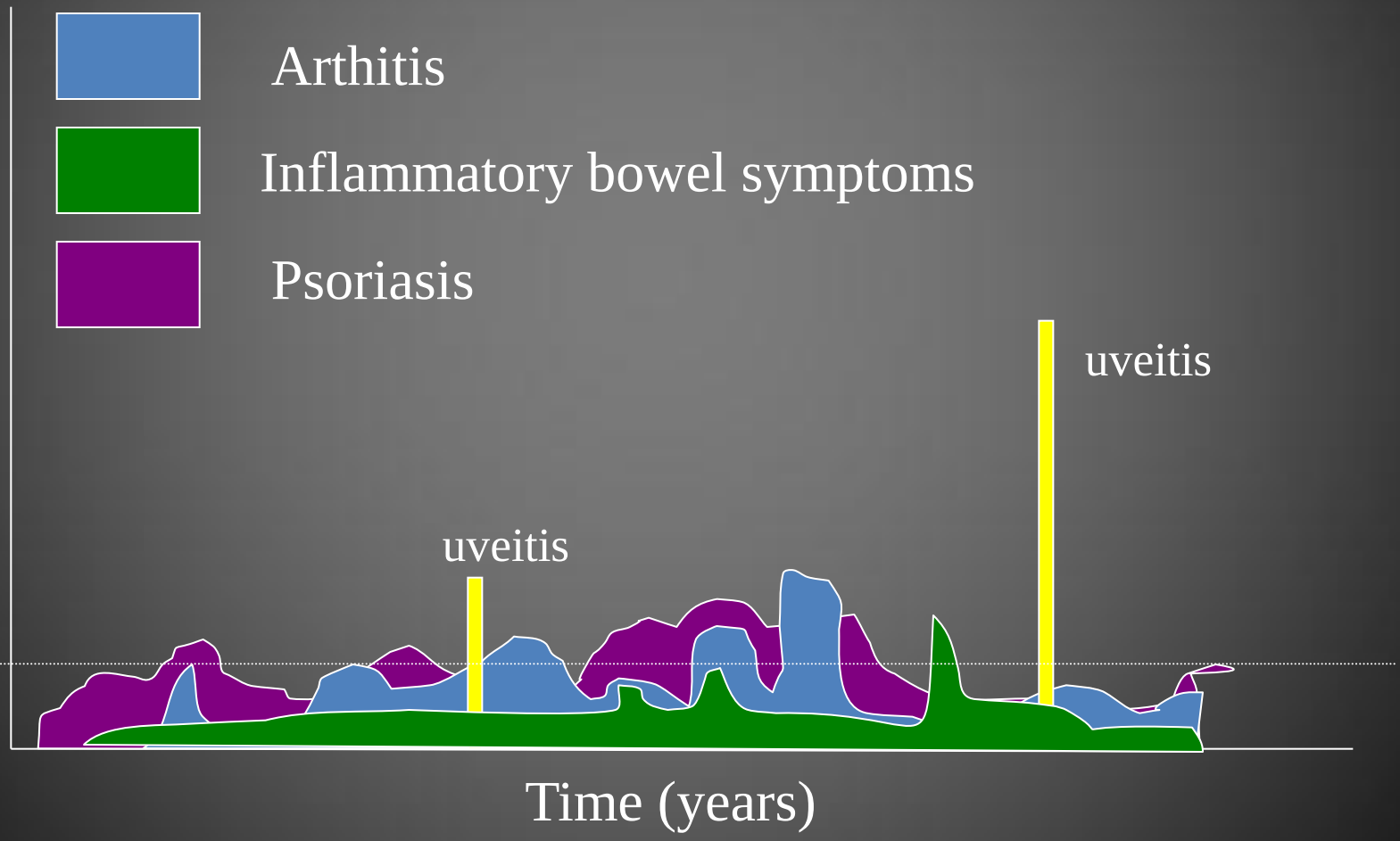
Features

HLA B27
Uveitis
Aortitis
Urethritis
IBD
Psoriasis

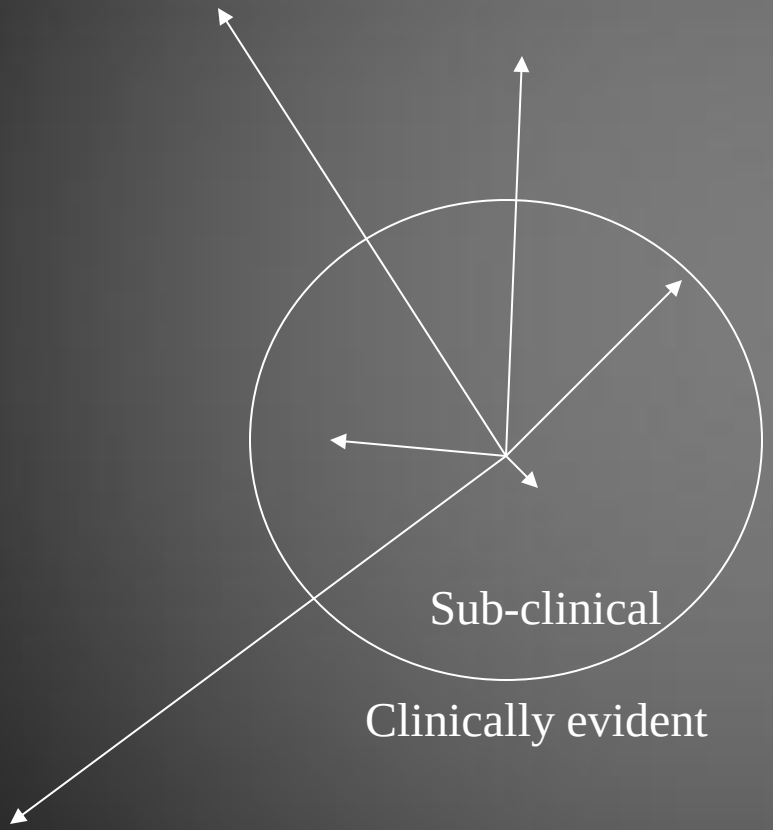
Features of Spondyloarthritis



Pattern of spondyloarthropathy



SpAs:
Common immunopathological mechanisms: variable expression

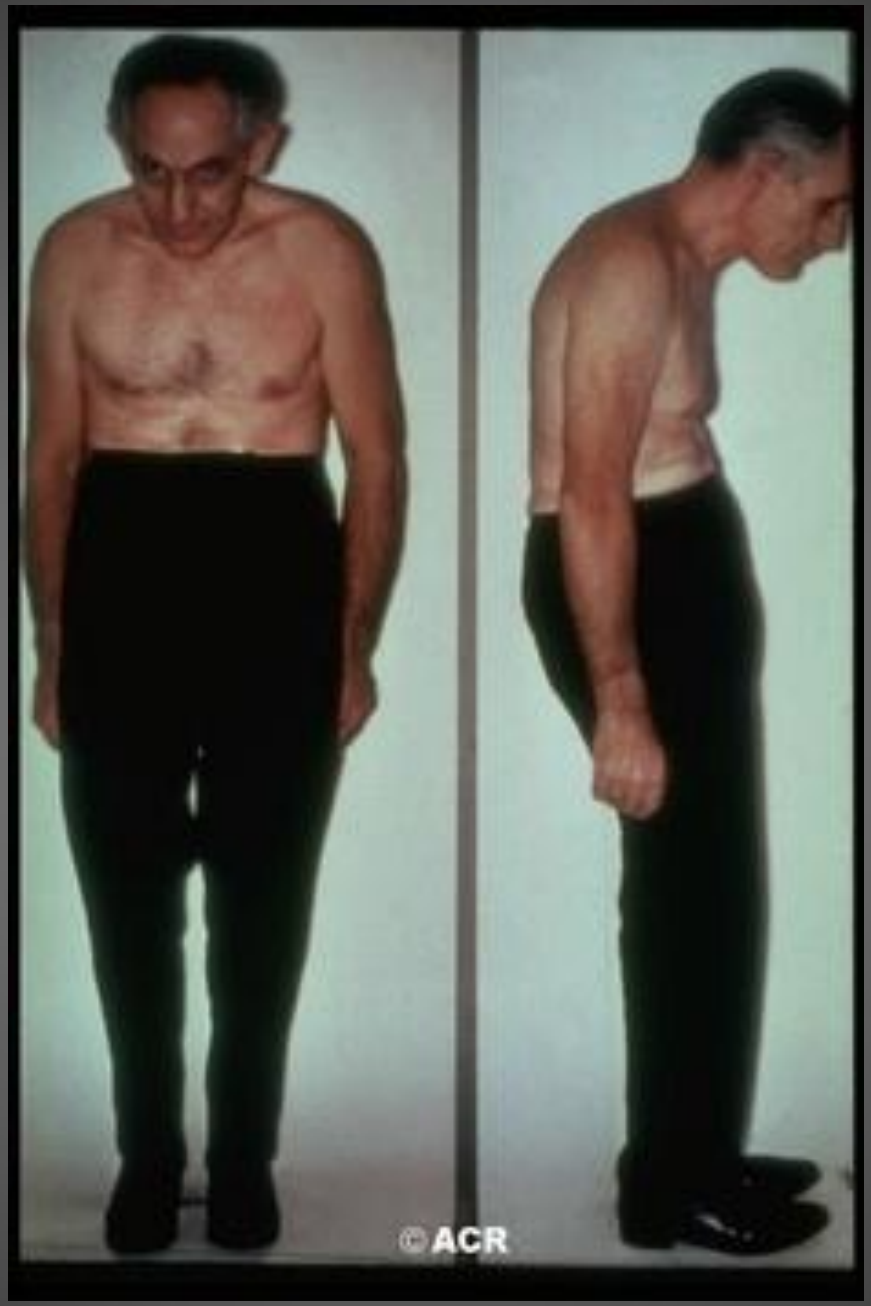


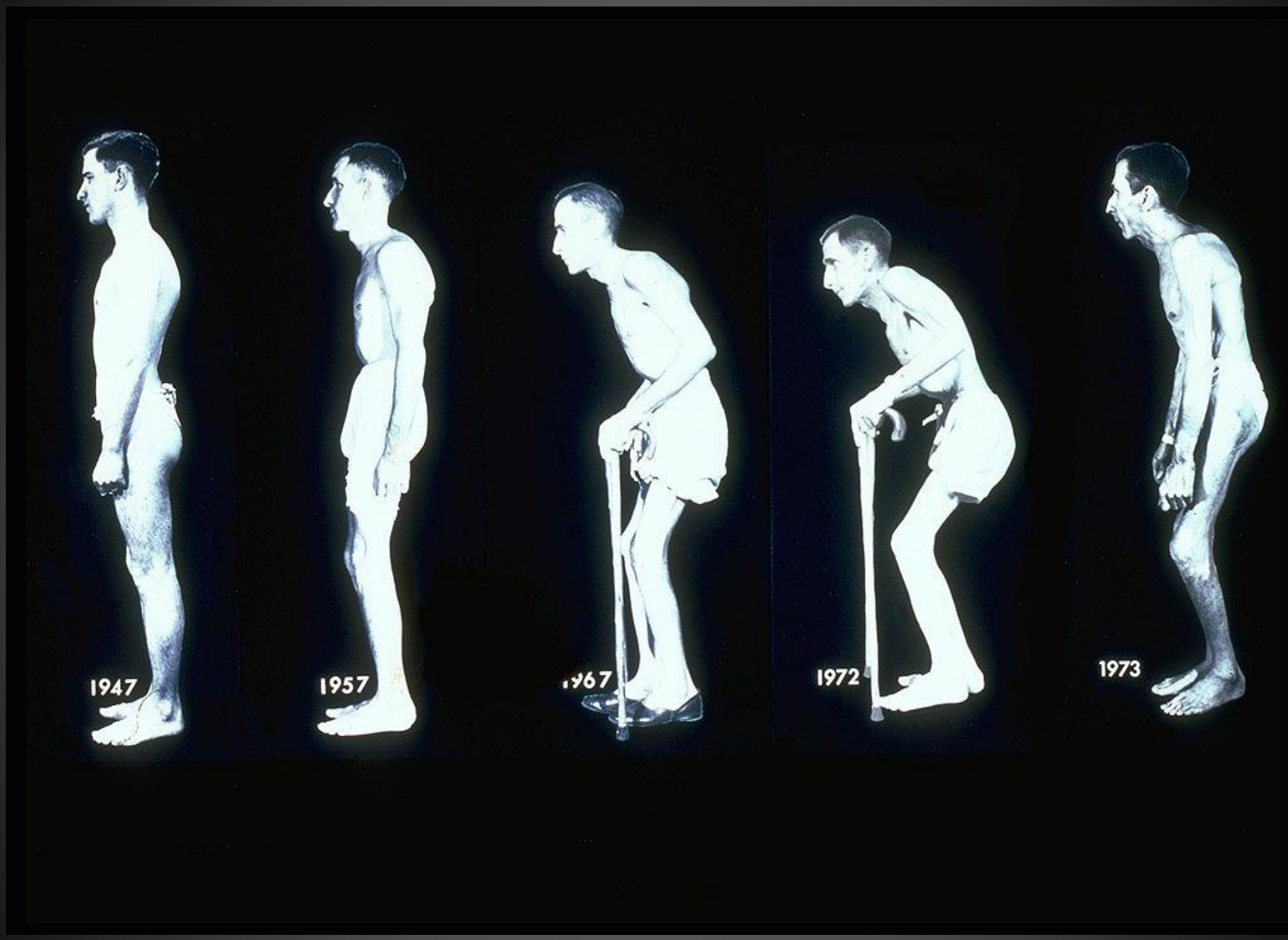
Would allow for:

- varying features of a single AI process
- discordant *symptoms* temporally
- distinct clinical features
- subclinical ‘disease’

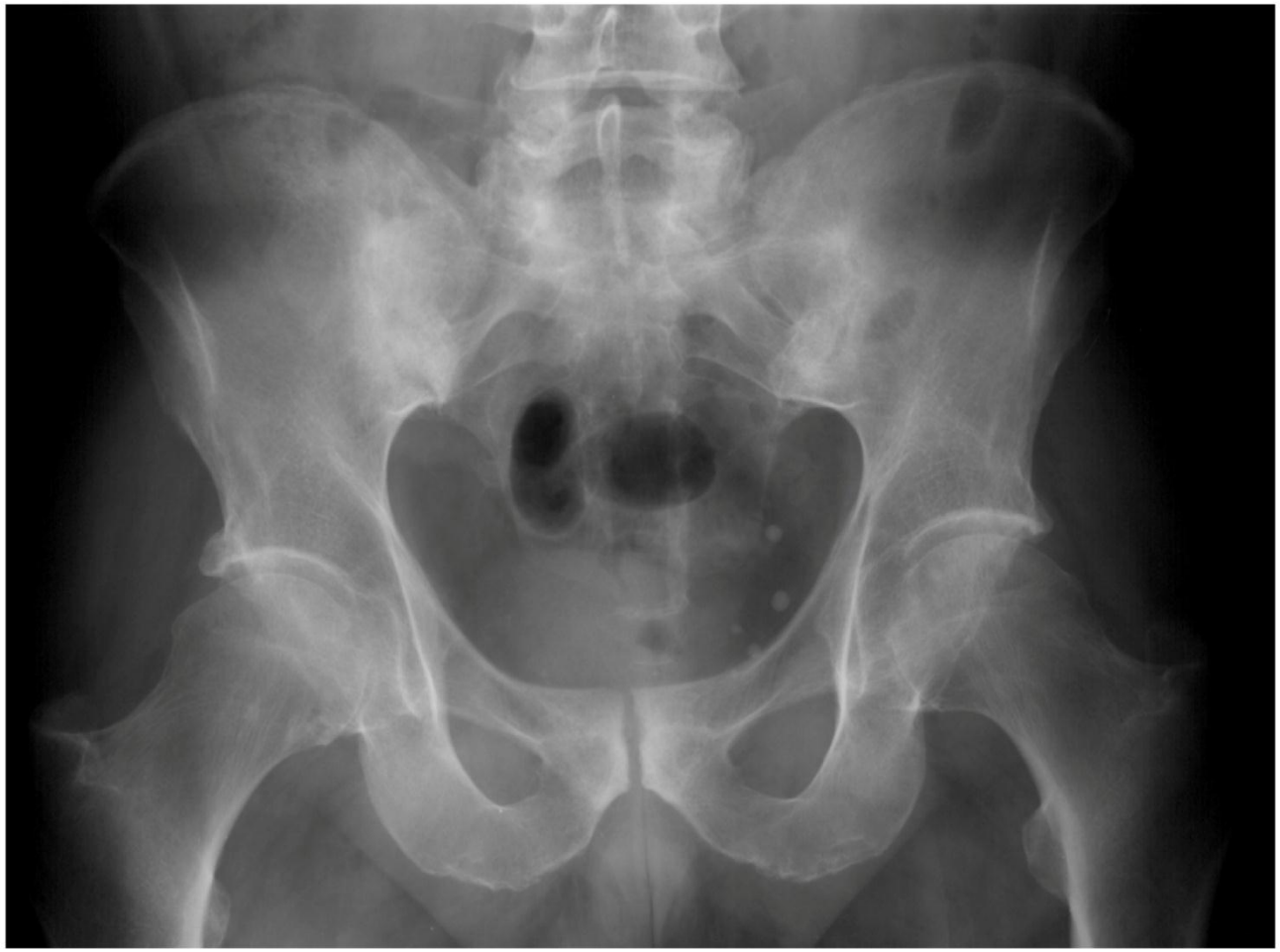
Ankylosing spondylitis

- Male preponderance
- Sacroiliitis
- Progressively stiffening spine
  - Vertebral squaring, syndesmophytes, discitis, enthesopathies and subenthesial osteitis
- Association with:
  - HLA B27
  - Uveitis
  - Peripheral joint synovitis/enthesitis
  - Inflammatory bowel (?clinically silent)


© ACR


1947
1957
1967
1972
1973

Sacroiliitis Grade 3 Bilaterally

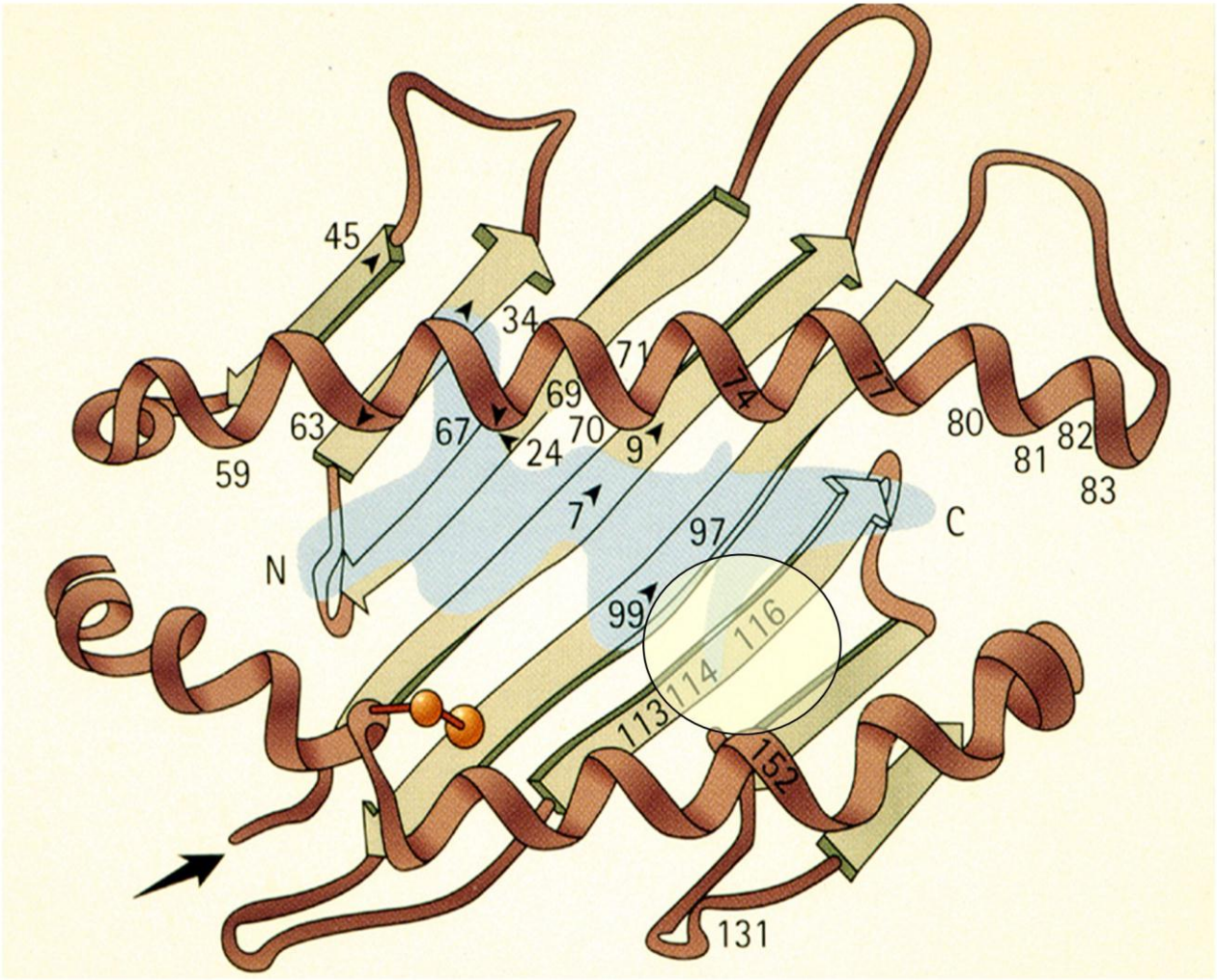


HLA-B27 associated diseases

- **Ankylosing spondylitis** 95%
- Arthritis associated with inflammatory bowel disease 15%
  - with spinal disease (AS) 50%
- Psoriatic arthritis 20%
  - with spinal disease (AS) 50%
- Reactive arthritis (post infection)
  - mild 30%
  - severe (or progressing to AS) 75%

Peptide-Binding Groove of HLA-B27

Disease predisposing B27 subtype *04 differs just in positions 114 and 116 from non-predisposing subtype *06



Khan MA: Spondyloarthropathies. In: Hunder G (Ed.). ATLAS OF RHEUMATOLOGY. 4rd Edition. Philadelphia, PA: Current Medicine 2005, pp. 151-180.(with permission)

What Is the Role of HLA-B27 in the Inheritance of Ankylosing Spondylitis?

- Only about 5% of B27-positive individuals develop AS.
- AS rarely recurs in families in the absence of HLA-B27, or in B27-negative members of AS-families.[1]
- Twin and family studies suggest that about half of the risk of developing AS is due to HLA-B27.[1,2]
- Thus B27 is almost essential for the inheritance of AS, but other genes determine which B27-positive cases develop the disease.

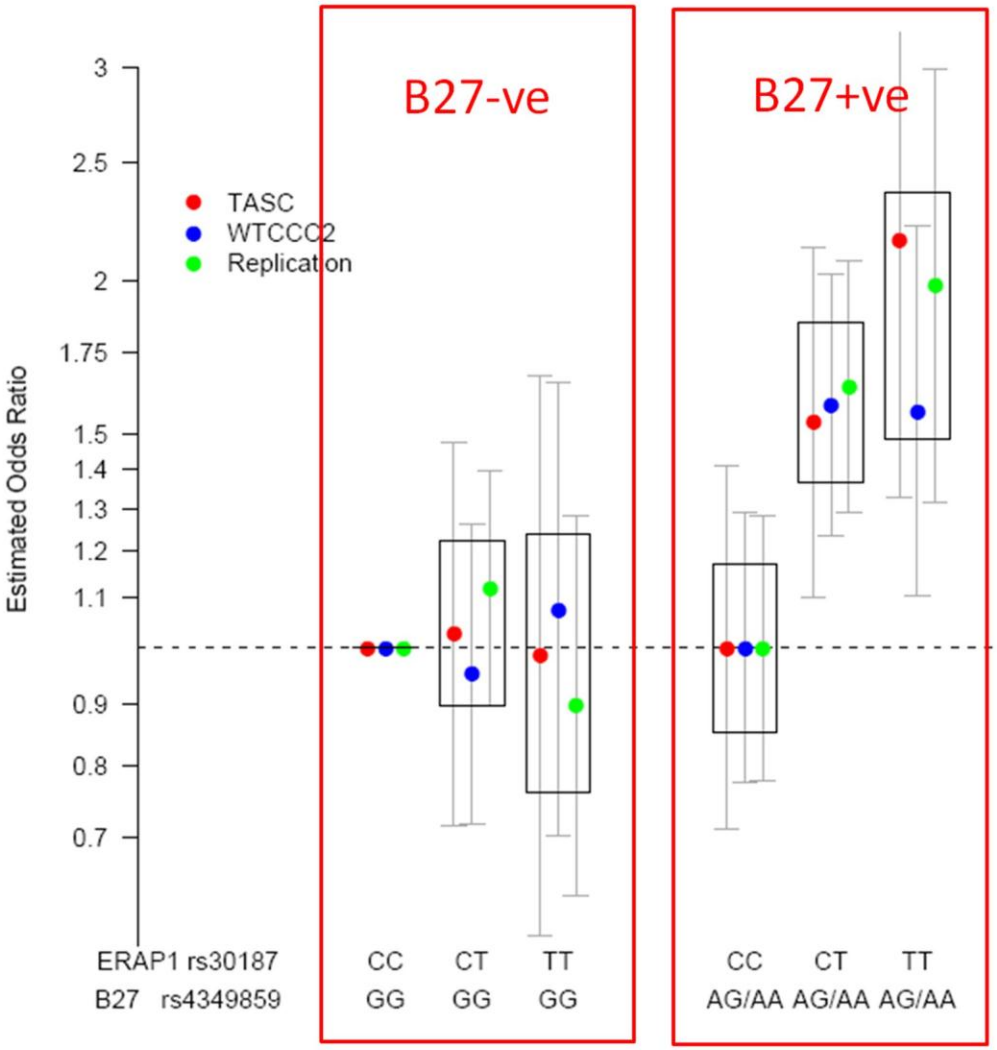
1. Laval SH, et al. Am J Hum Genet 2001;68:918-26
2. Brown MA, et al. Arthritis Rheum 1997;40:1823-8

ASAS

AS genetics

- AS is a polygenic disease!
- The protein encoded by ERAP1 is an aminopeptidase involved in trimming HLA class I-binding precursors so that they can be presented on MHC class I molecules. The encoded protein acts as a monomer or as a heterodimer with ERAP2
- ERAP1 has the 2nd strongest genetic association with AS after HLA-B27.
- HLA-B27 and ERAP1 are synergistic in susceptibility to both AS and psoriasis.
- ERAP1 variants alter peptide handling in the endoplasmic reticulum;
- Modulation of ERAP1 function has therapeutic potential in AS;

ERAP1 is only associated with HLA-B27 positive AS

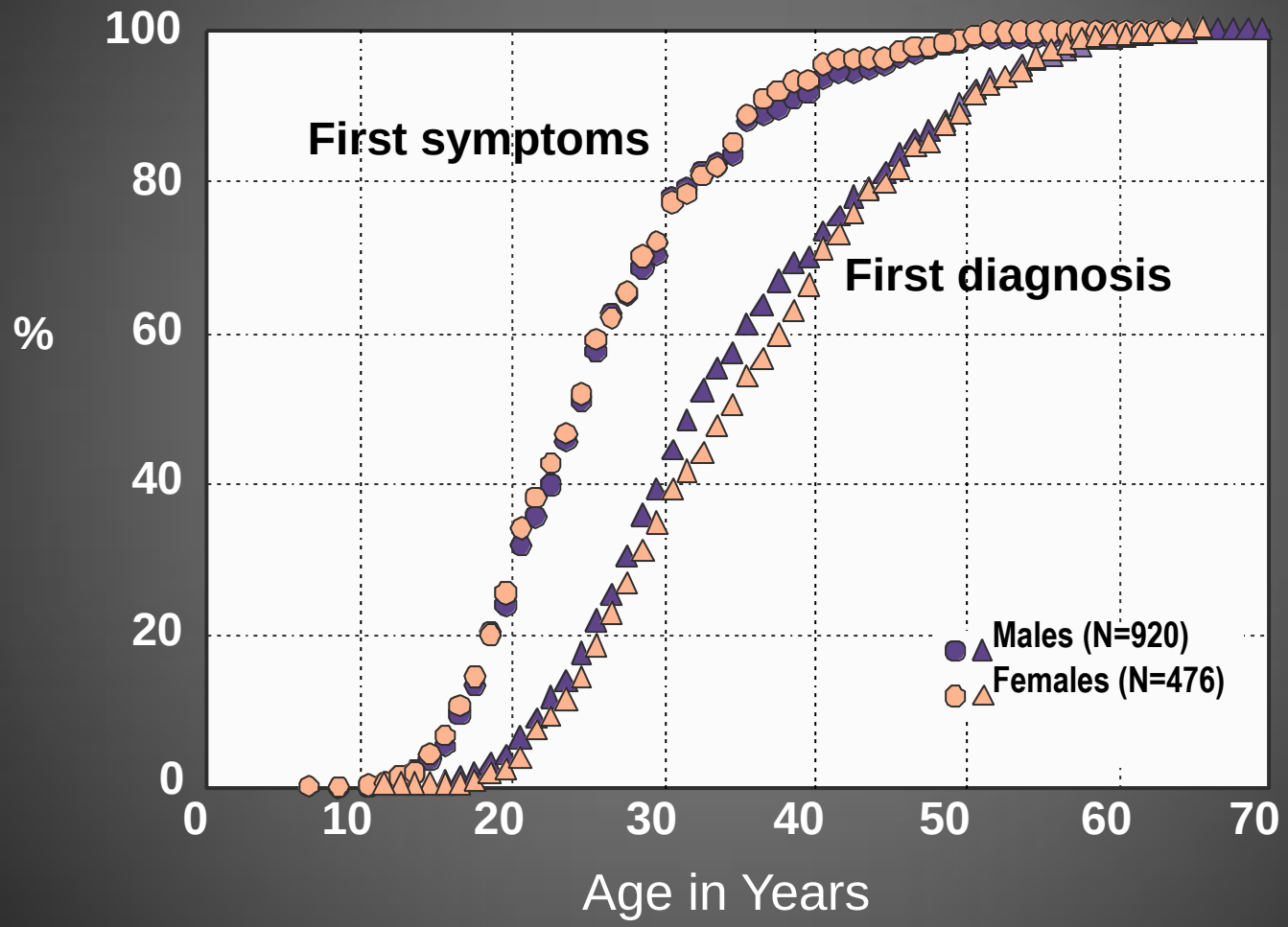


Evans DM et al. Nat Genet 2011;43:761-7 (with permission)

Immunopathogenesis: AS theories

- B27+ selects and directs excessive antigen presentation;
- Non thymic deletion of self-reacting T cells
- Abnormal processing of antigen (ERAP1);
- B27 as a recognised self peptide (heavy chain misfolding, x-reactive epitope, heavy chain recognition by NK cells);

Age at First Symptoms and at First Diagnosis in AS Patients



Delay in diagnosis: 8.5-11 years

Delay in AS diagnosis

- Men don’t present to doctors;
- Back pain is often protocolised by Primary Care doctors;
- Hx of Inflammatory Back pain not taken
- Imaging for back pain is seldom done;
- Radiographic signs are late or subtle on conventional views;
- Radiological signs are not identified;

Inflammatory back (and neck) pain

- Chronic pain >3 months
- Morning stiffness >30 minutes
- Improvement with movement
- Disturbed sleep (second part of the night)
- Buttock pains (often alternating)

1:20 of back pain cases

Important to assess all patients with back pain accordingly, especially the young and middle aged

ASAS classification criteria for axial SpA in patients with back pain for more than 3 months and age at onset less than 45 years

(Rudwaleit M et al Ann Rheum Dis 2009;68:777-83)

ASAS classification criteria for axial 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
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's/colitis
- Good response to NSAIDs
- Family history of SpA
- HLA-B27
- Elevated CRP

***Sacroiliitis on imaging**

- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- Definite radiographic sacroiliitis according to modified NY criteria

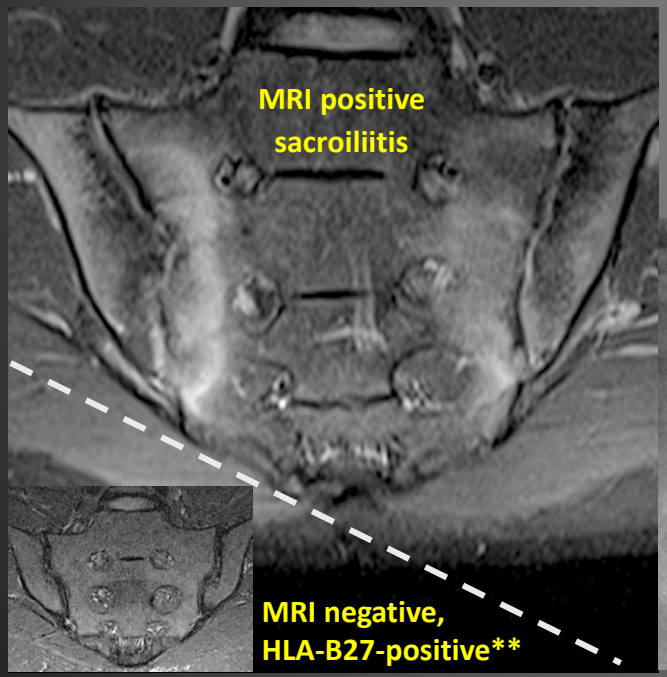
Spectrum of Axial Spondyloarthritis

Patients with chronic back pain ≥3 months and aged <45 years

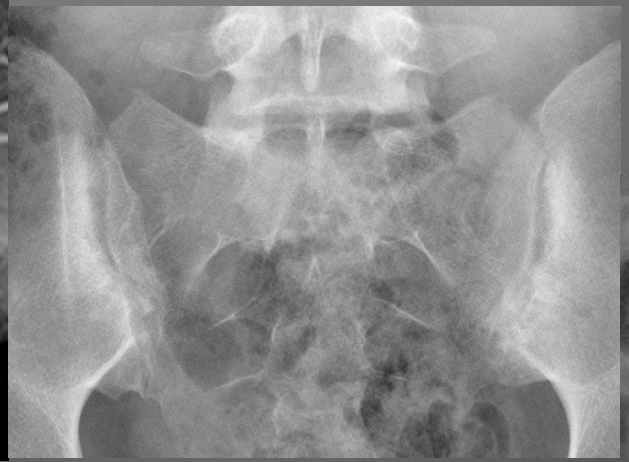
Axial SpA (ASAS criteria)

Non-radiographic stage
X-ray-negative

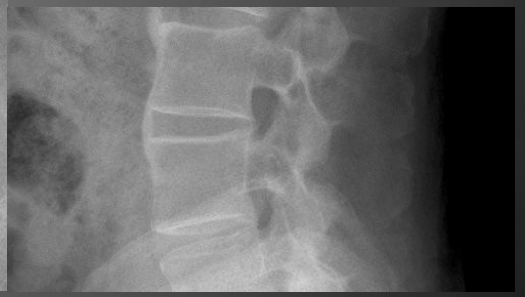
Ankylosing Spondylitis (modified New York criteria)



Radiographic stage
X-ray-positive sacroiliitis



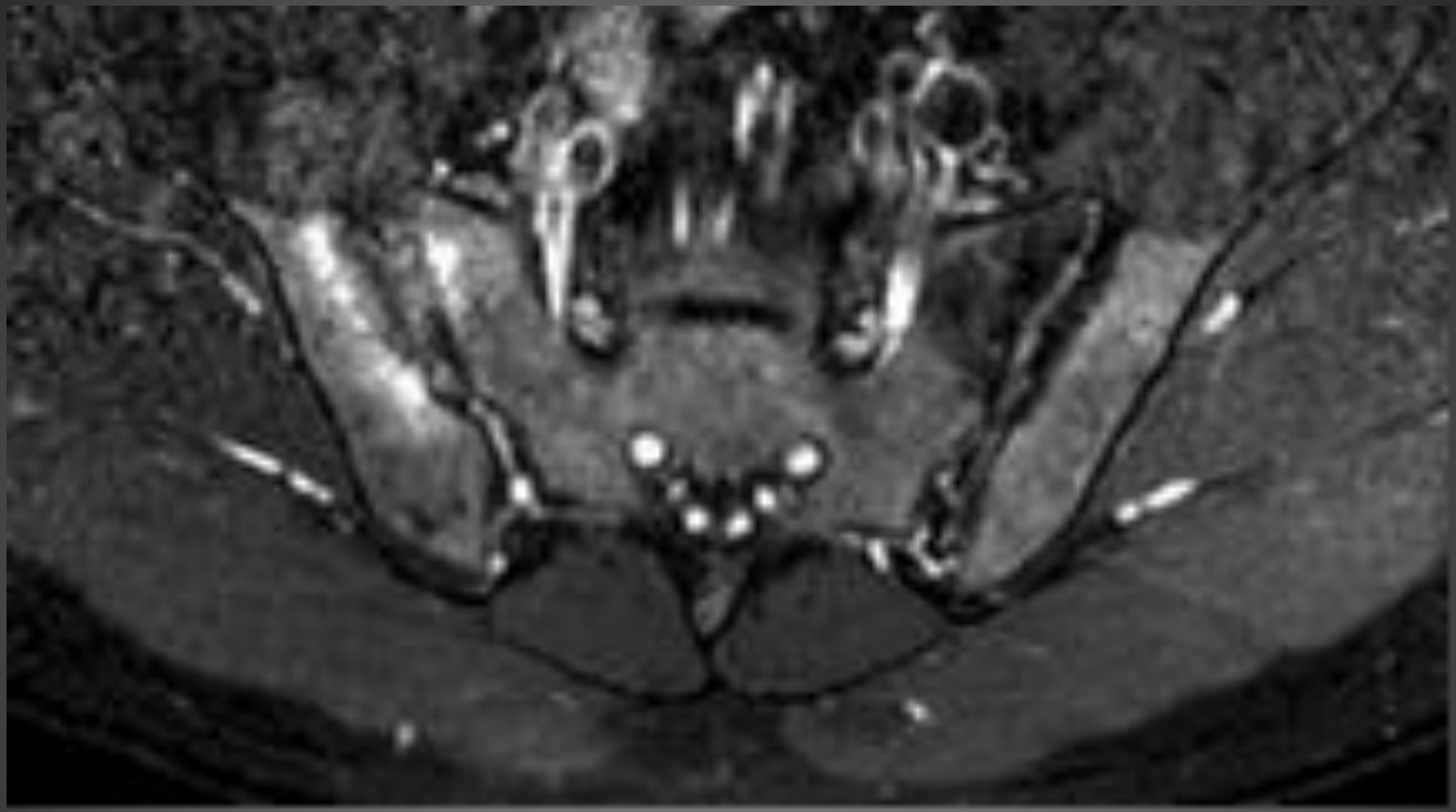
Radiographic stage
X-ray-positive sacroiliitis and/or spinal changes***



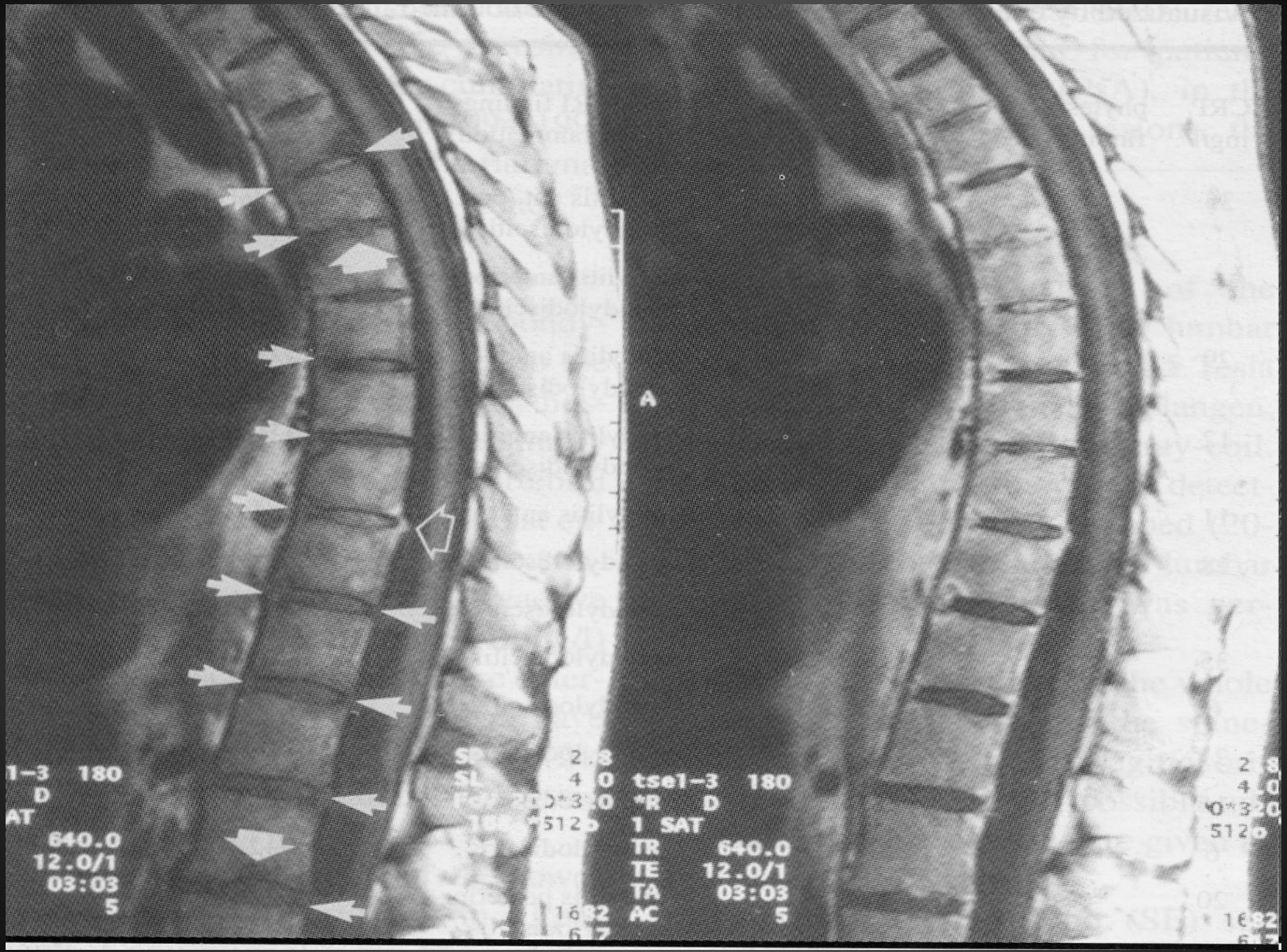
Estimated proportion of affected individuals*

Time

* Heights reflect an estimate of the proportion of patients in each group
** Clinical arm if non-radiographic axial SpA
*** Radiographic evidence if inflammatory spinal changes including i.e., syndesmophytes, fusion or posterior element involvement



MR evidence for sacroiliitis. Relatively sensitive for identifying current SIJ inflammation – identifies pre-radiographic sacroiliitis. Will not date pathology.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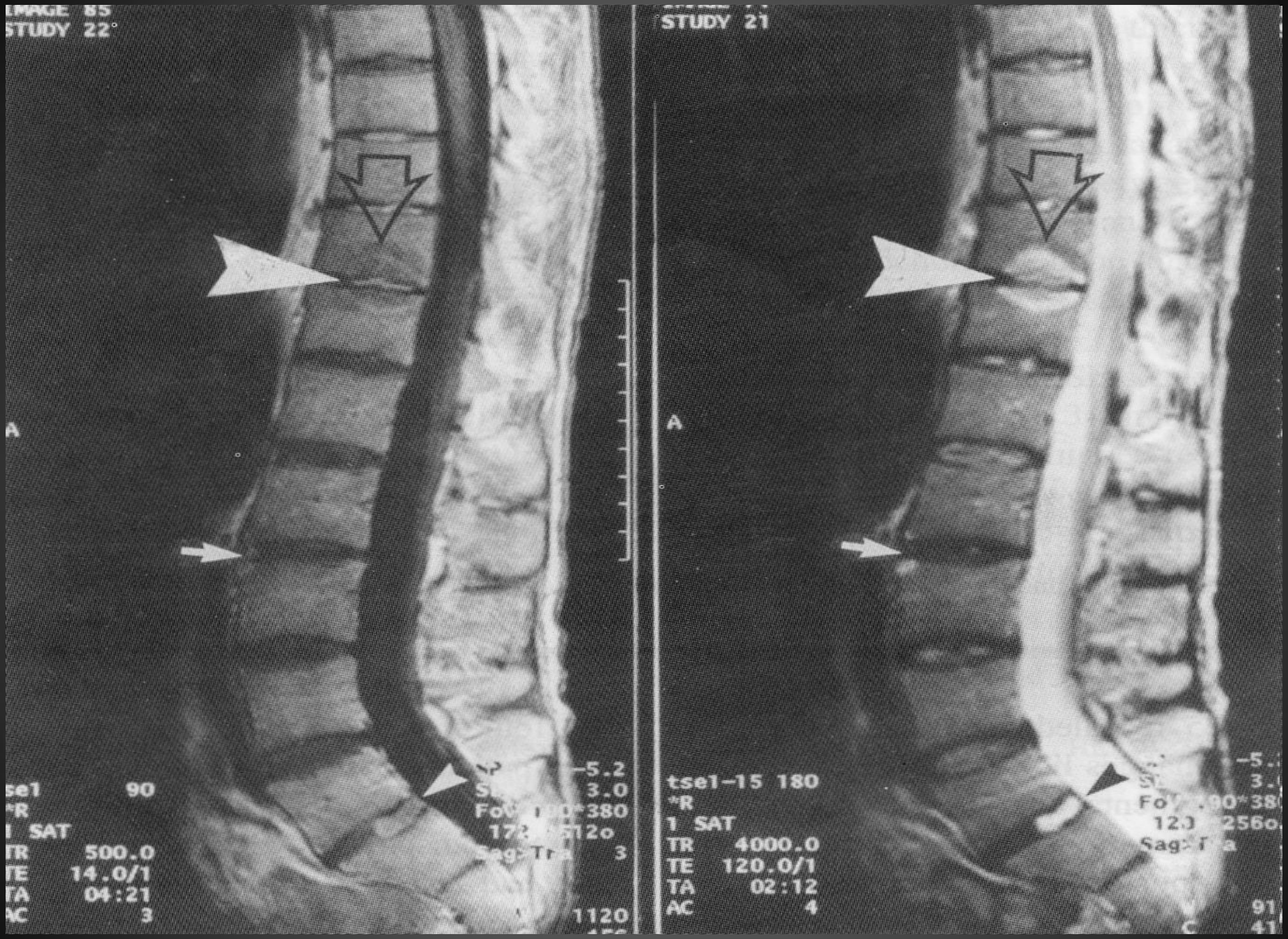
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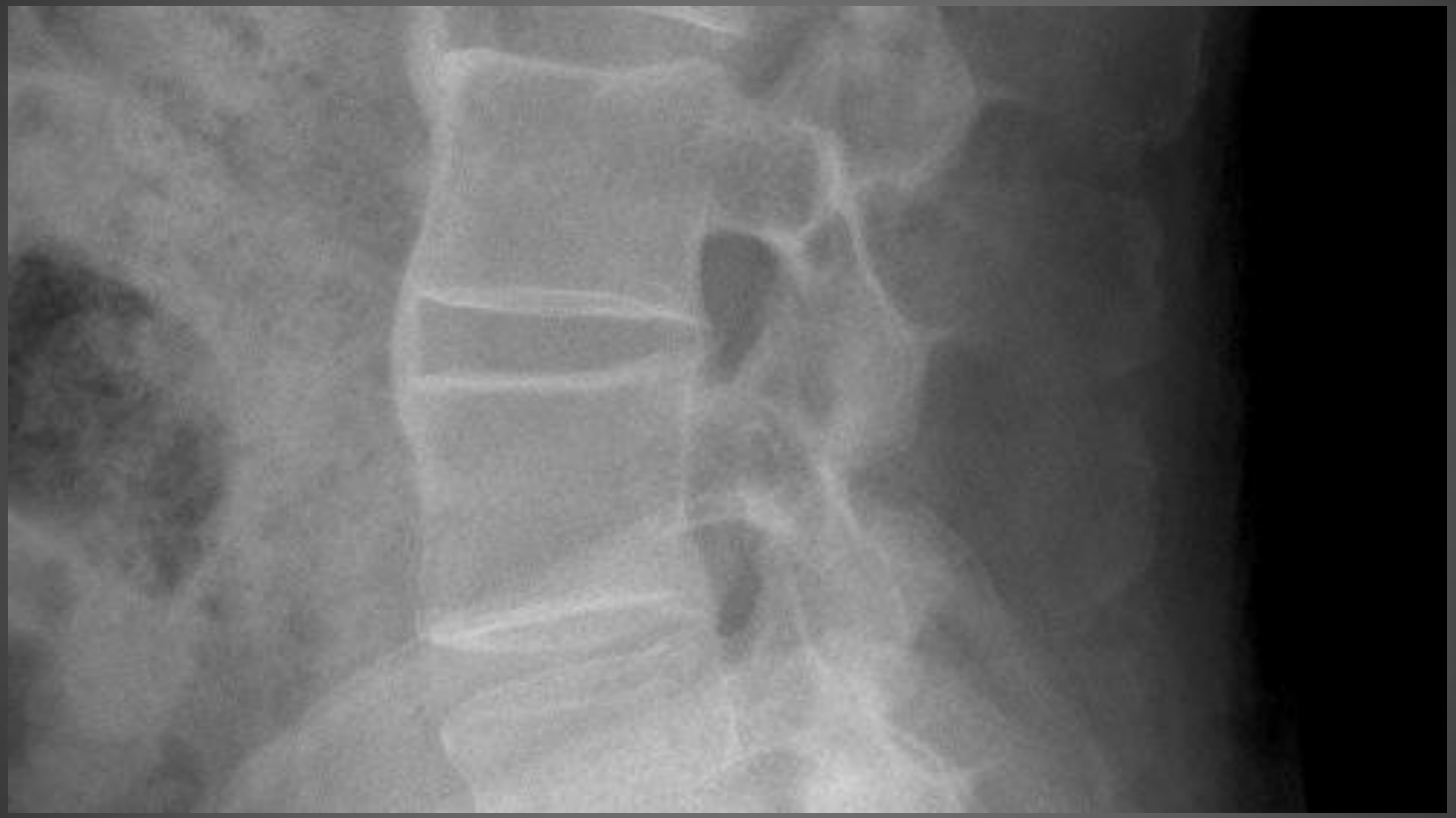
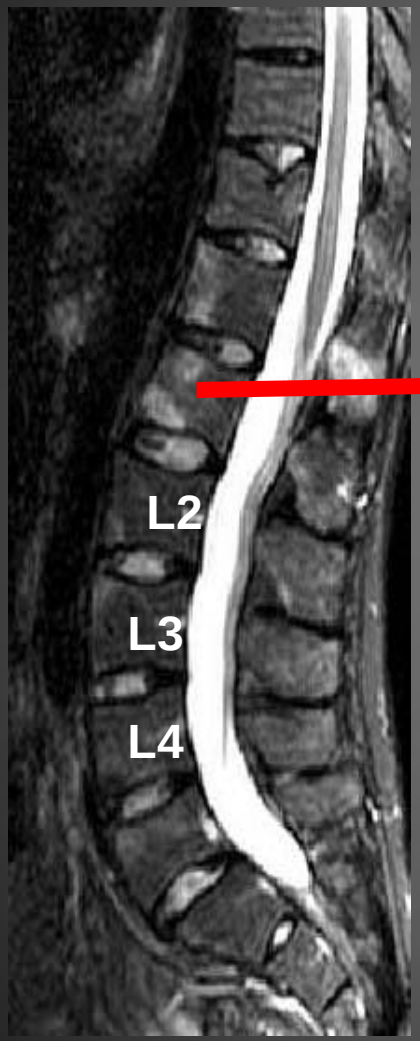
Anterior Longitudinal Ligament
Calcification in AS



Syndesmophyte
Marginal or paramarginal (eg DISH)

Link between spinal inflammation and new bone formation in AS

(n=39)

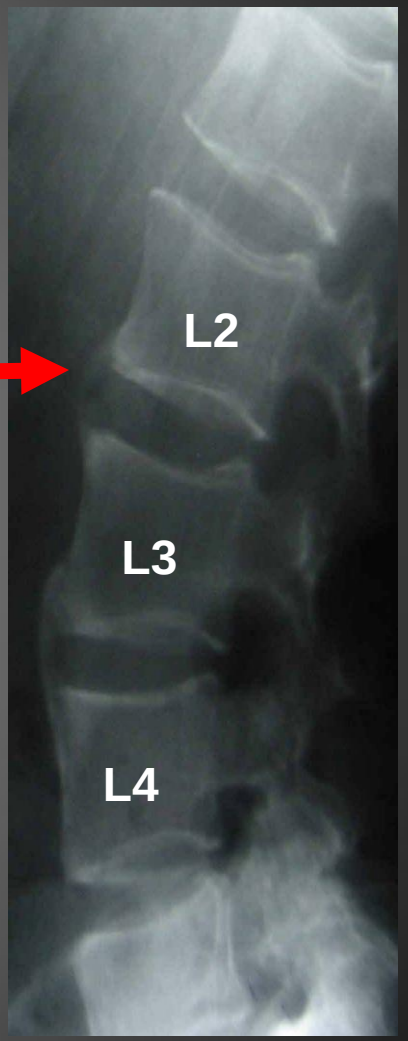


6.5 % ***(10 syndesmophytes developed from 153 VEs with inflammation)***

p = 0.006

OR: 3.3 (95% CI: 1.5 – 7.4)

2.1 % ***(16 syndesmophytes developed from 769 VEs without inflammation)***



STIR MRI – inflammation at baseline

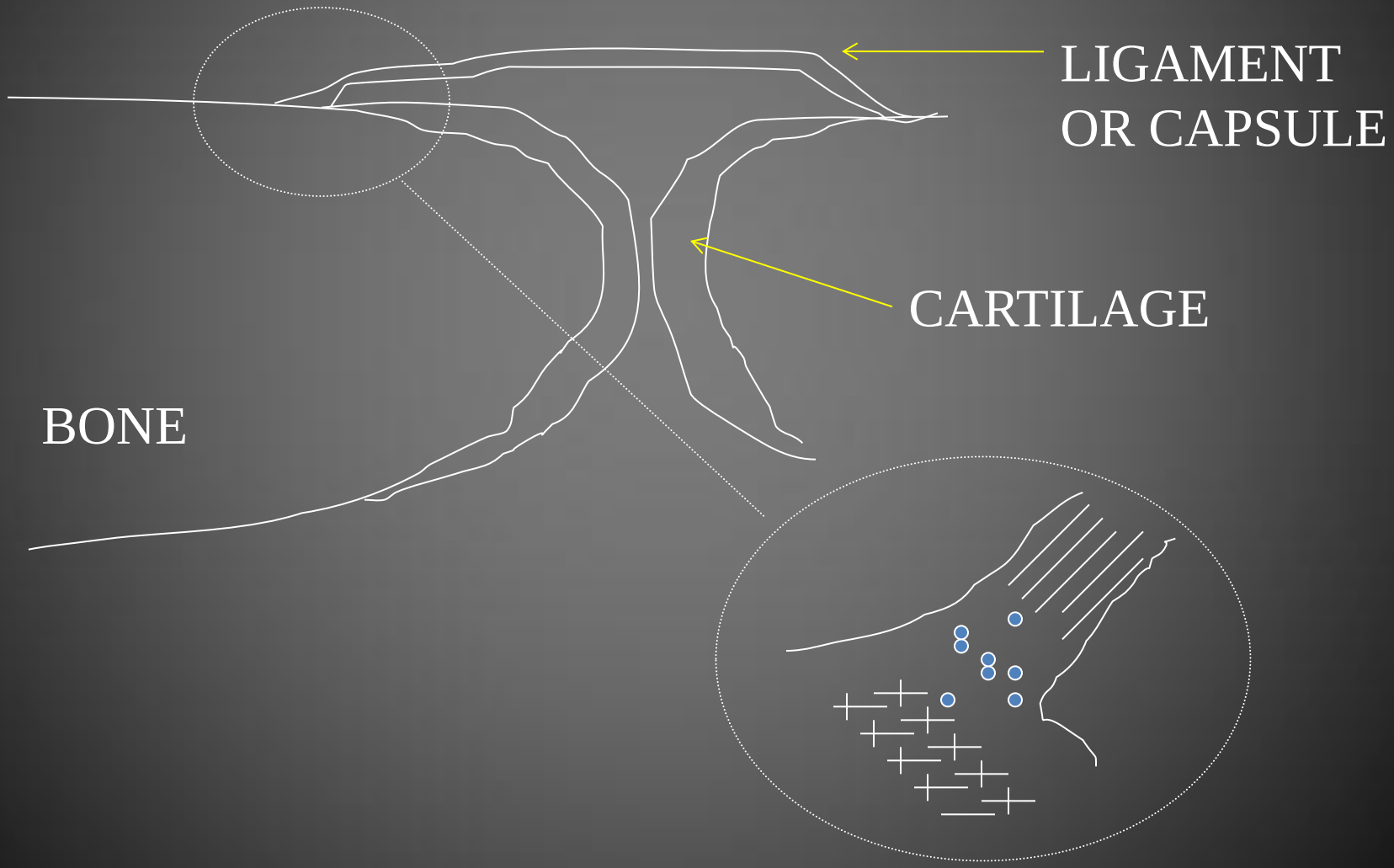
Syndesmophyte formation – after 2 years of anti-TNF

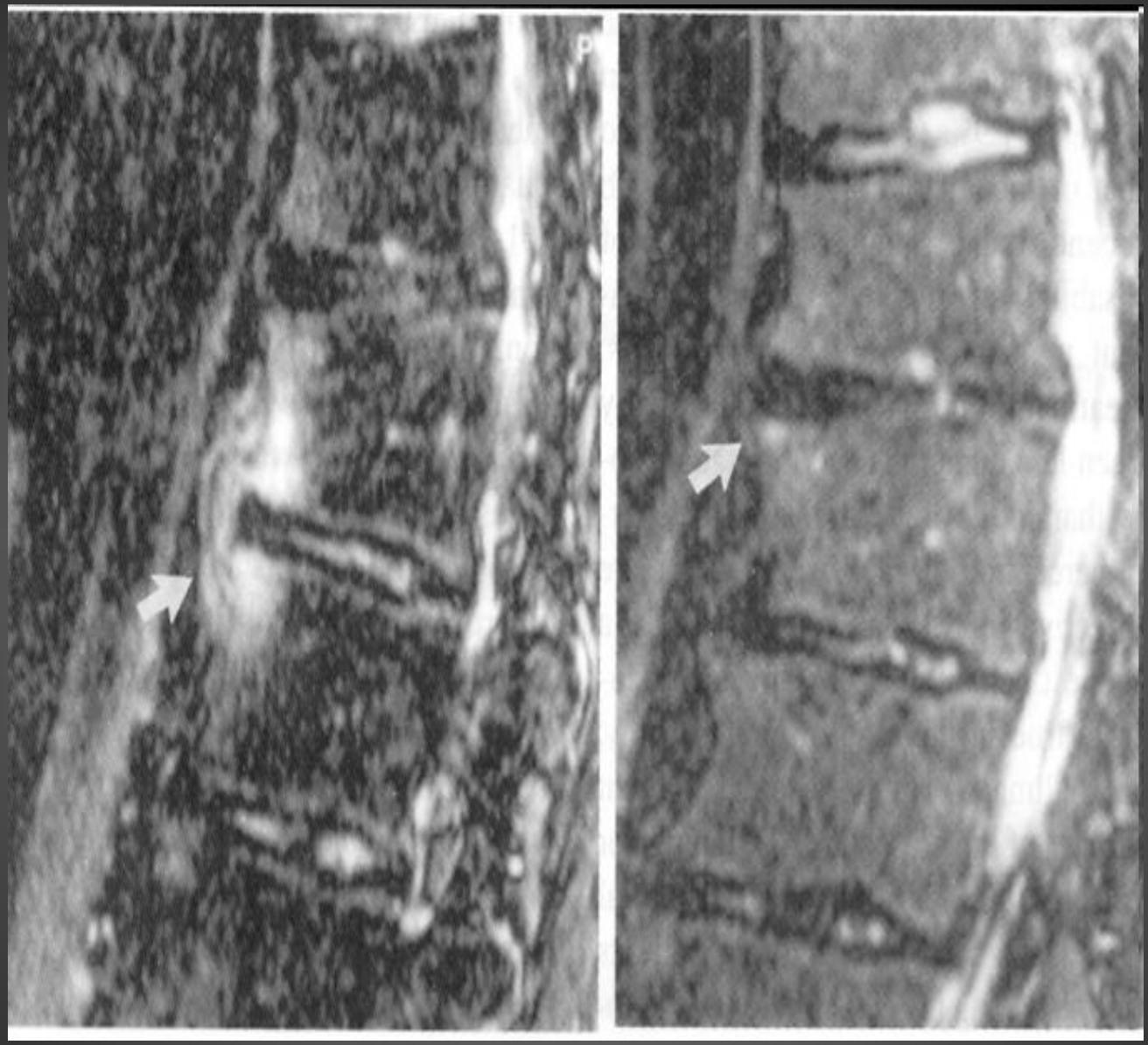
Baraliakos X, Arthritis Res Ther. 2008 Sep 1;10(5):R104

Enthesis: Definitions

- An enthesis: the attachment of ligaments or tendons to bone
- Enthesopathy: abnormal or pathological changes at an enthesis (includes enthesophytes)
- Enthesitis: inflammation at an enthesis. Imaged as inflammation and can be associated with osteitis or periostitis at adjacent bone

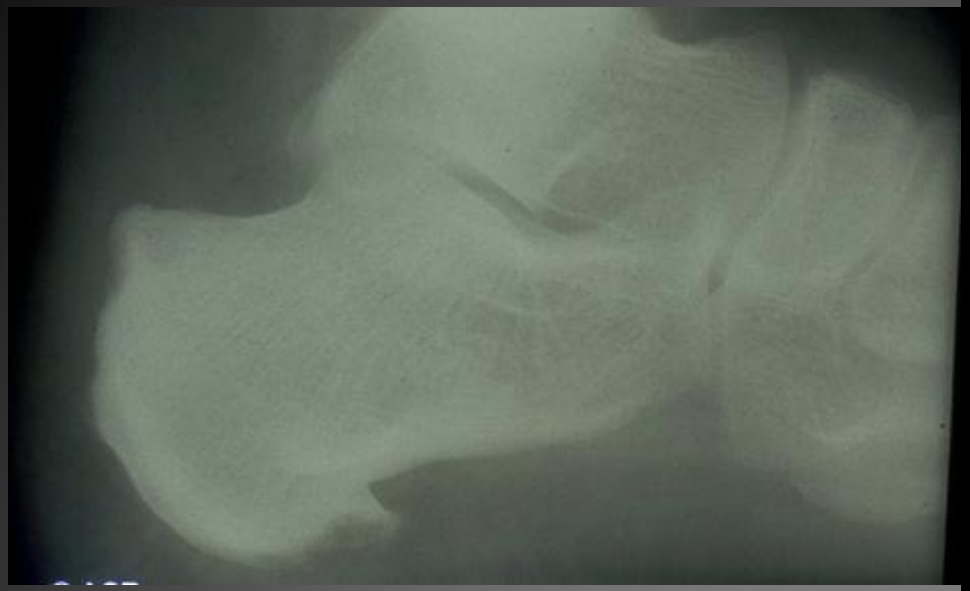
An Enthesis

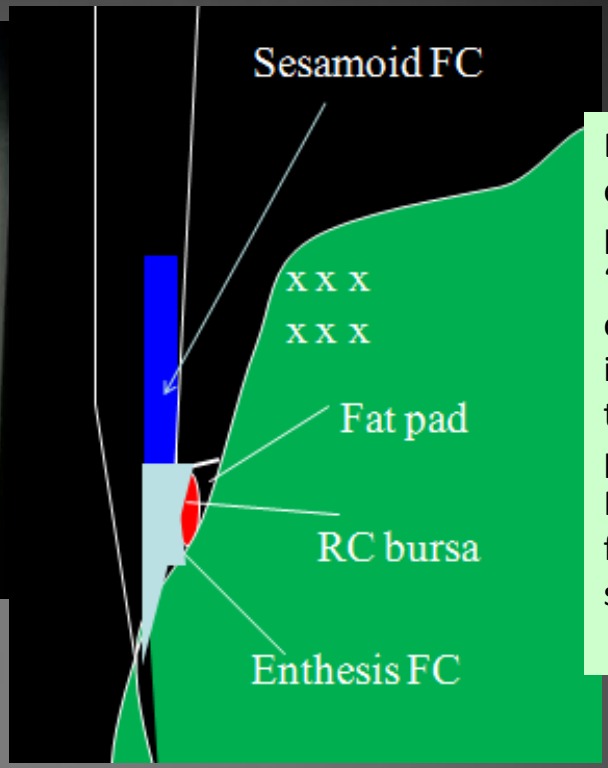




Entheses

- Are rich in fibrocartilage (FC), except some fibrous entheses – often insertional into diaphyseal periosteum
- FC forms in tendons and ligaments at sites of shear stress
- Entheses are often part of an ‘enthesis organ’ which includes tendon and periosteal FC, bursae, folds of synovium





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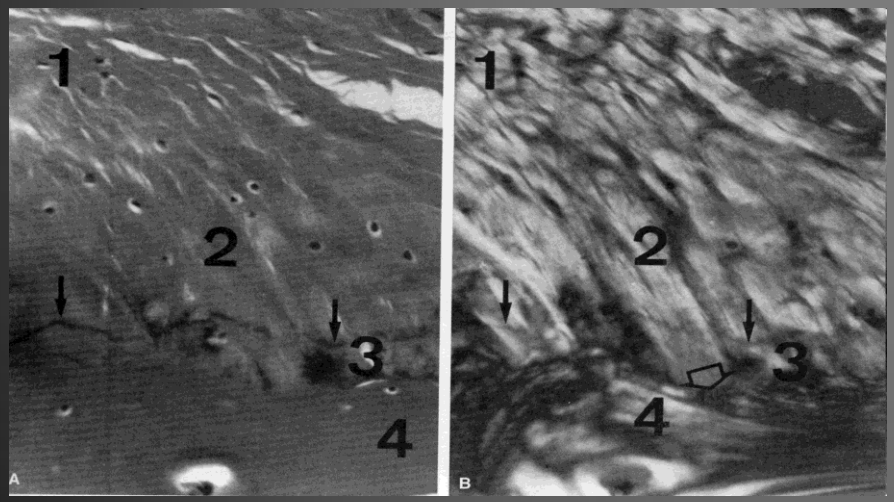

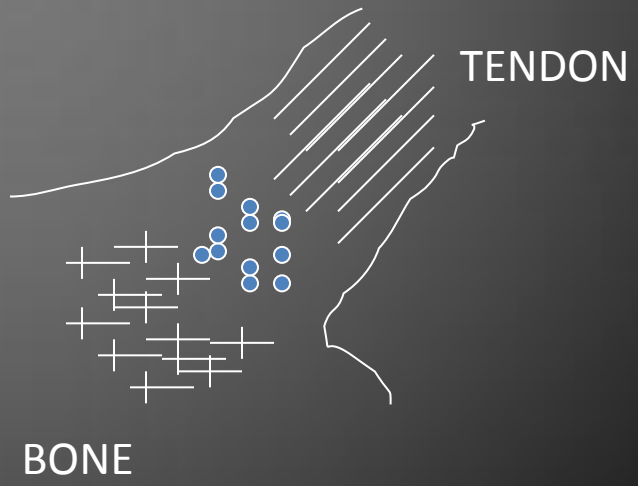

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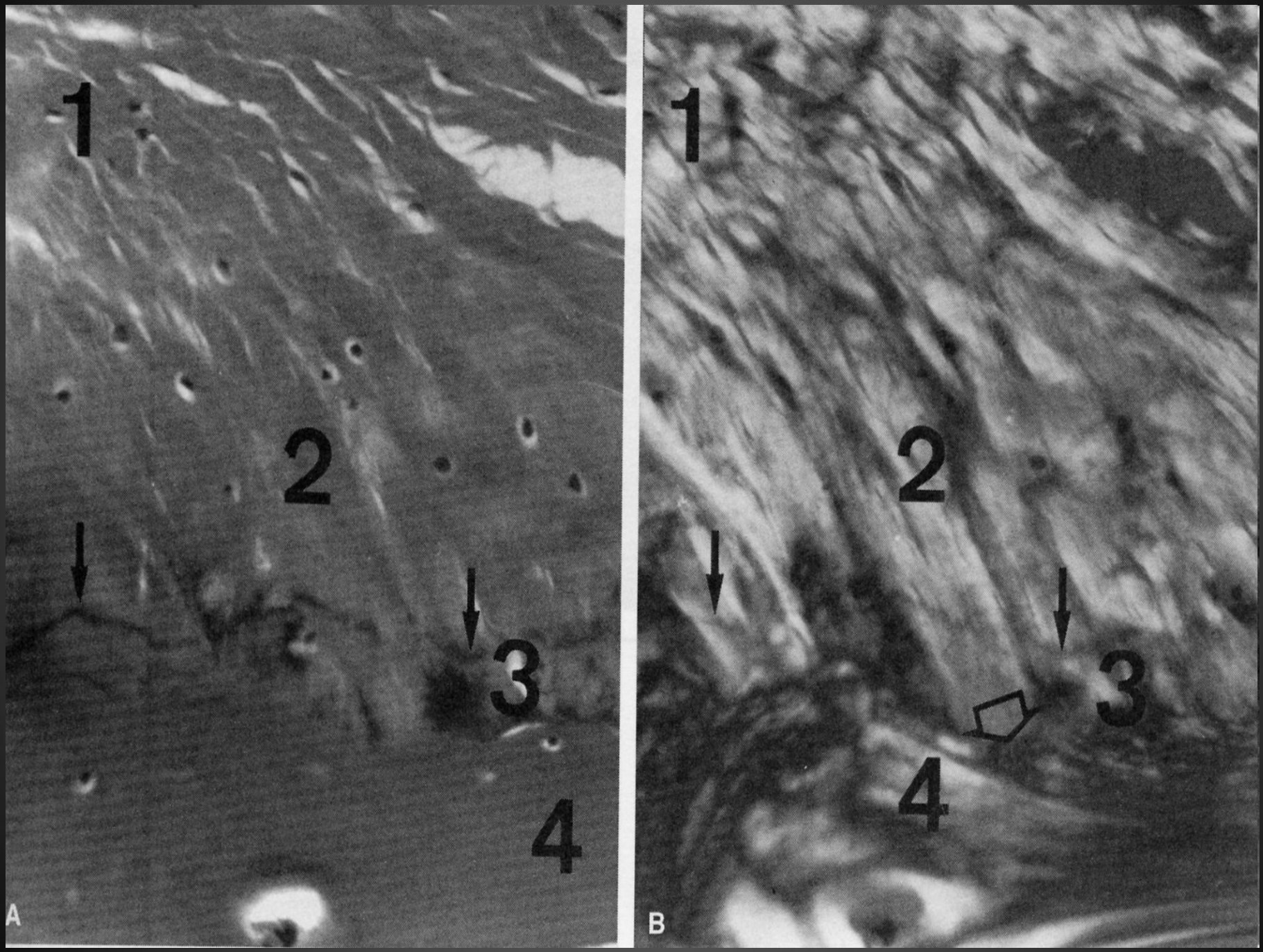
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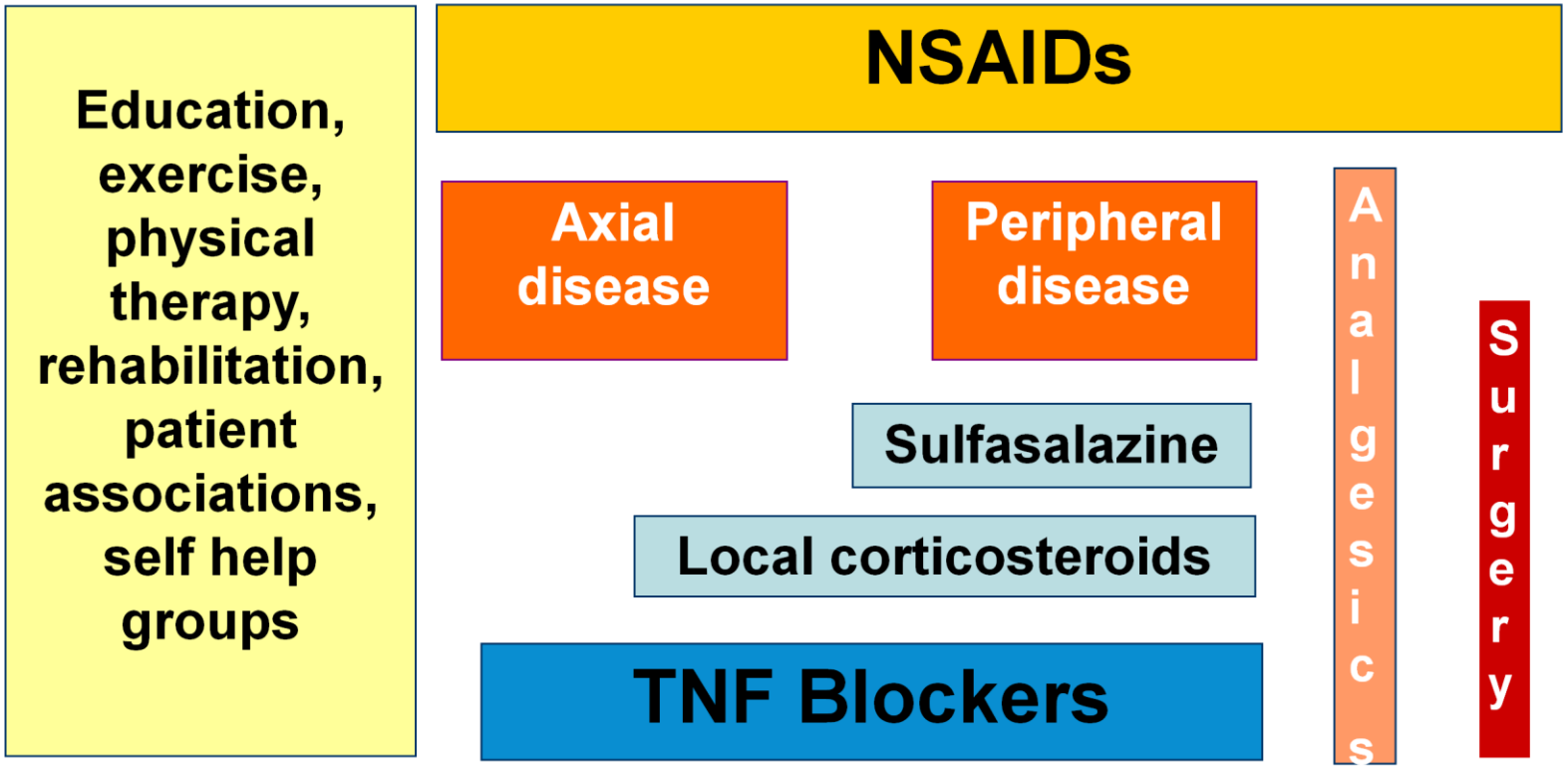
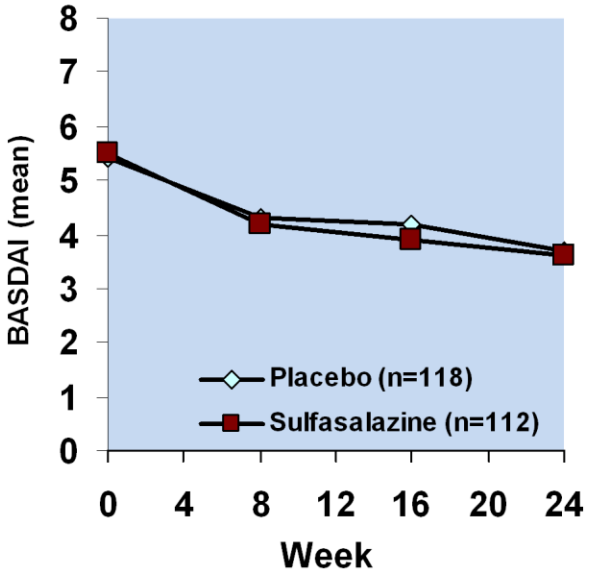
ASAS/EULAR Recommendations for the Management of Ankylosing Spondylitis



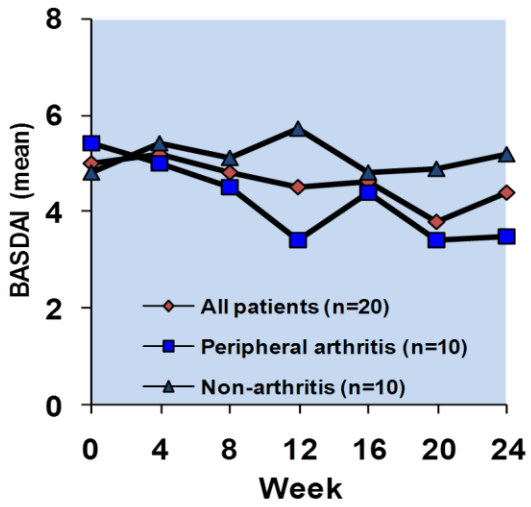
Zochling J et al. Ann Rheum Dis 2006;65:442-52 (with permission)

Conventional DMARDs Are Largely Not Effective for the Treatment of Patients with AS

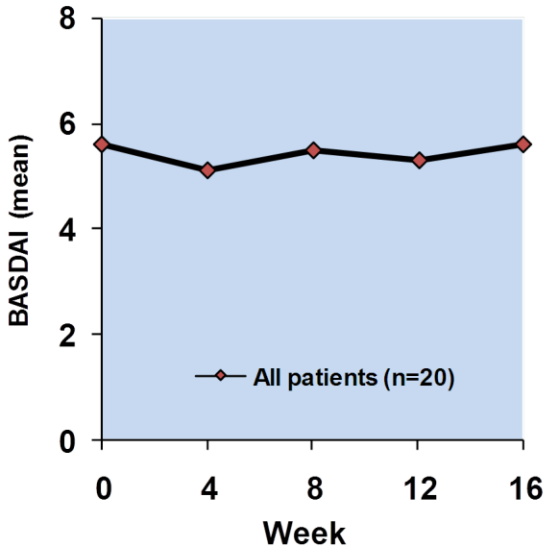
Sulfasalazine[1]
2 g/day



Leflunomide[2]
20 mg/day

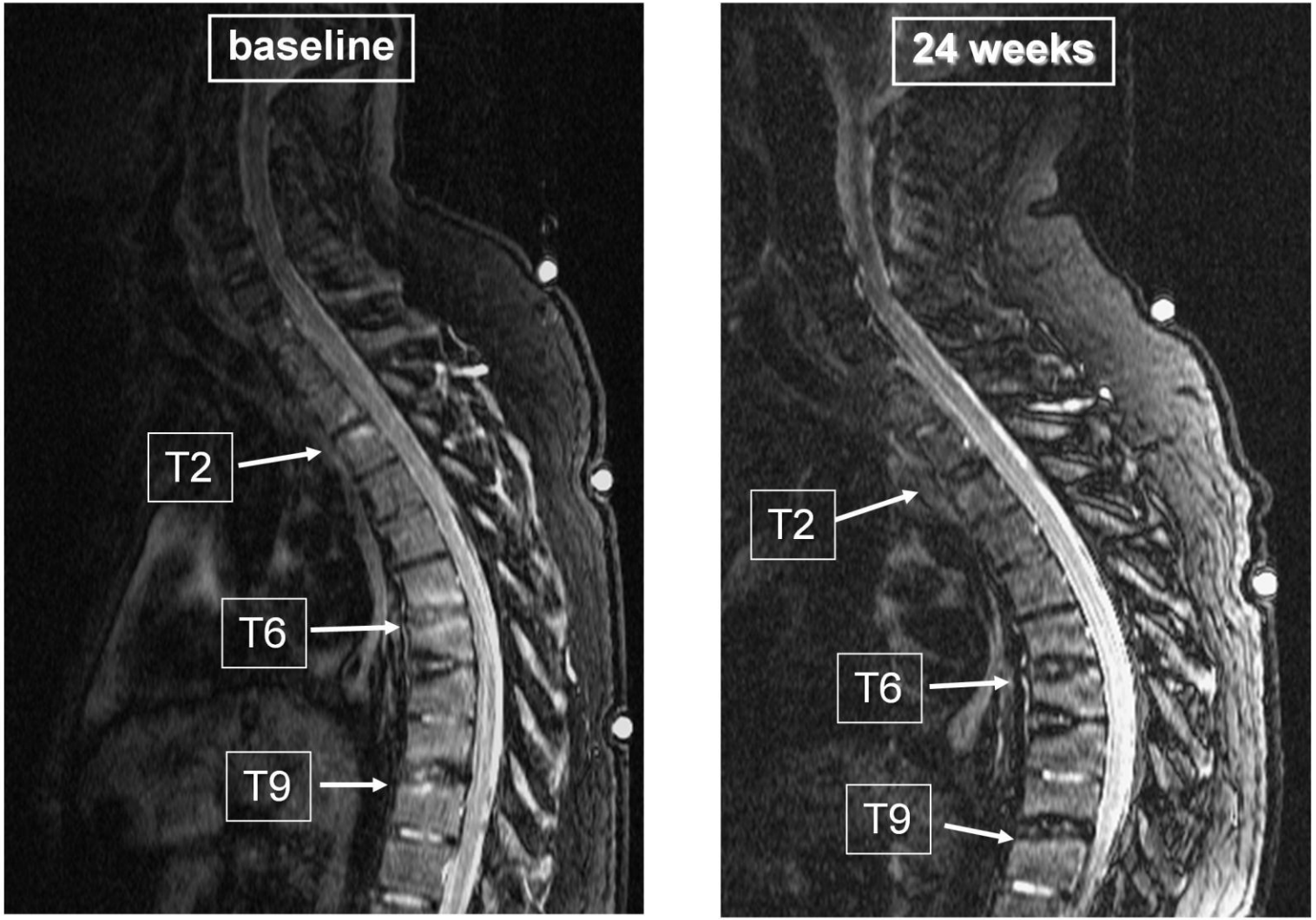


Methotrexate[3]
20 mg/week sc



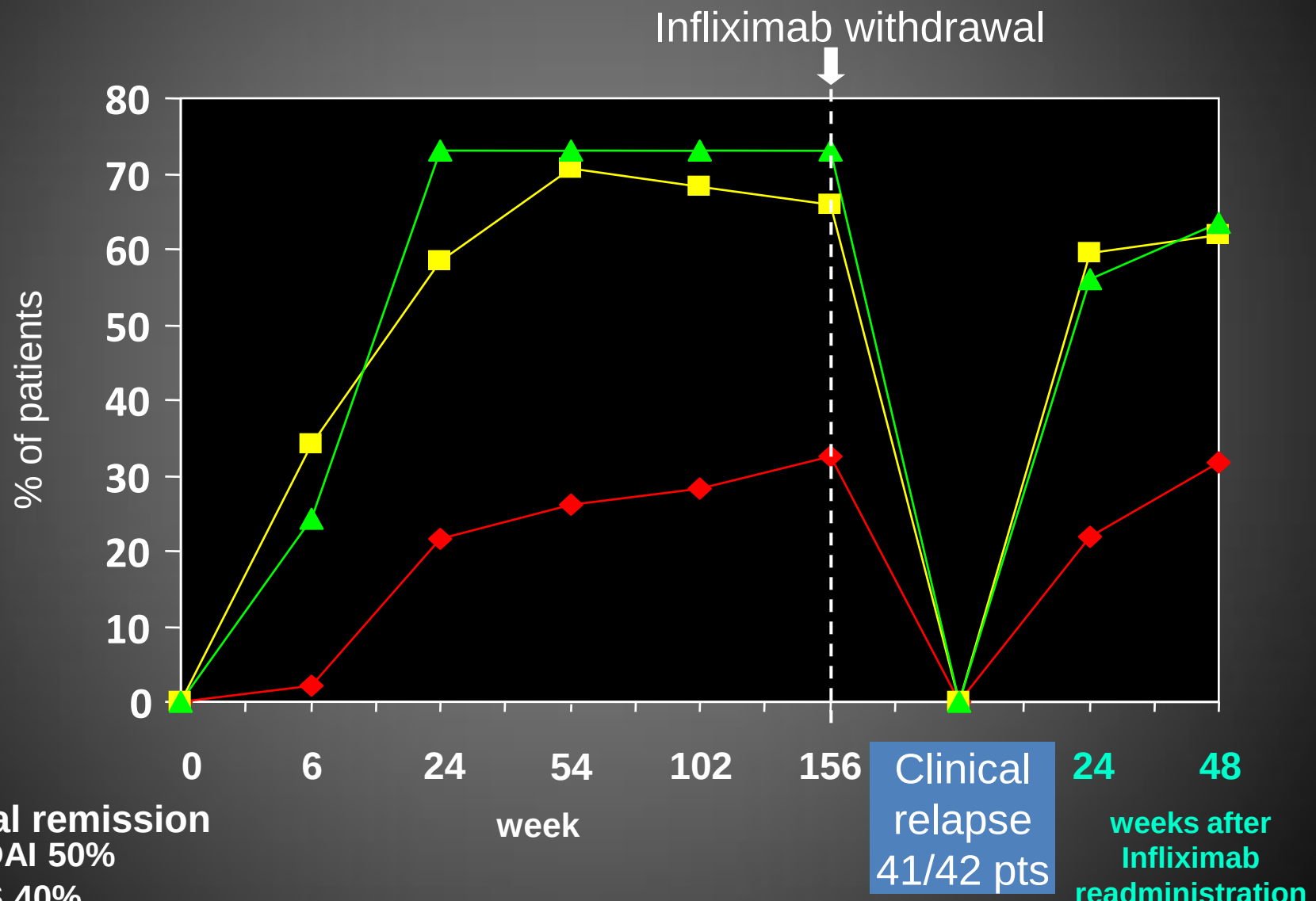
1. Braun J et al. Ann Rheum Dis 2006;65:1147-53
2. Haibel H et al. Ann Rheum Dis 2005;64:124-6.
3. Haibel H et al. Ann Rheum Dis. 2007;66:419-21.

ASSERT MRI Study: Example, Patient Before vs. After Therapy with Infliximab, STIR-Technique



Braun J et al. Arthritis Rheum 2006;54:1646-52 (with permission)

Relapse after cessation of infliximab therapy



Baraliakos et al., J Rheumatol. 2007 Mar;34(3):510

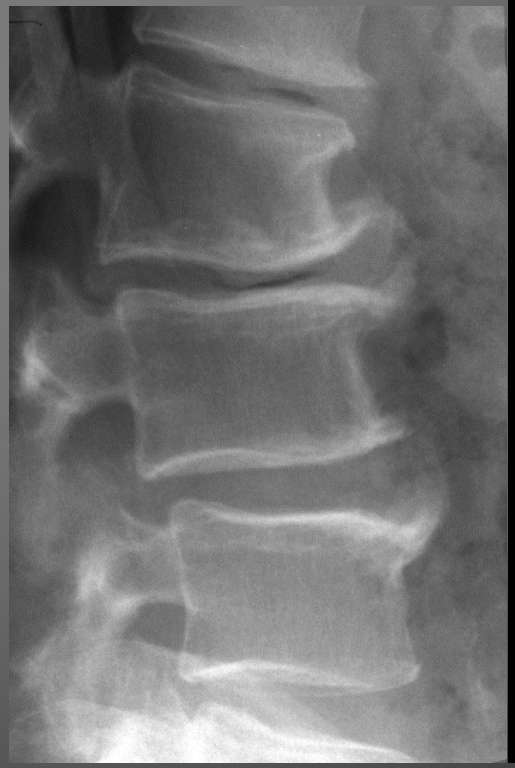
Does spinal inflammation precede syndesmophytes and does anti-TNFα stop/reduce the process?

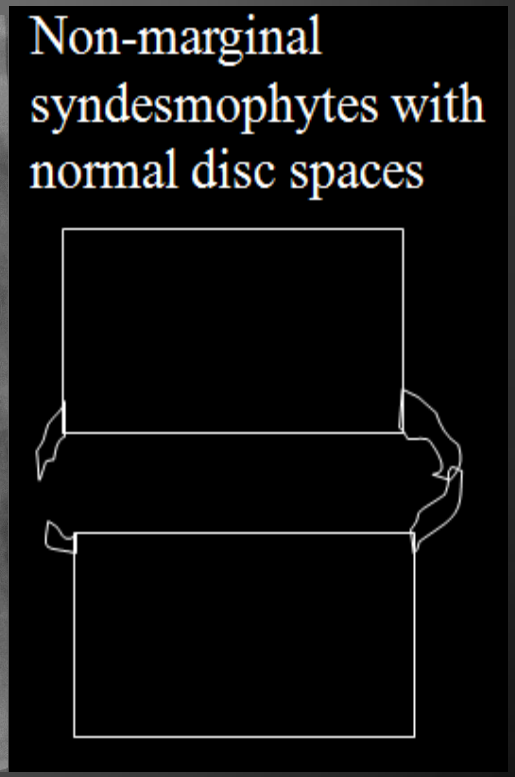
Ann Rheum Dis. 2012 Mar;71(3):369-73. doi: 10.1136/annrheumdis-2011-200208. Epub 2011 Oct 6.

MRI inflammation at the vertebral unit only marginally predicts new syndesmophyte formation: a multilevel analysis in patients with ankylosing spondylitis.

van der Heijde D[1], Machado P, Braun J, Hermann KG, Baraliakos X, Hsu B, Baker D, Landewé R.

- There is a slightly increased probability of developing syndesmophytes in vertebral units with MRI-defined osteitis (OR 1.51 – 2.26)
- Growth of existing syndesmophytes at the vertebral level was not associated with osteitis
- The large majority of new syndesmophytes develop in vertebrae without inflammation





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Rheumatology (Oxford). 2013 Apr;52(4):718-26. doi: 10.1093/rheumatology/kes364. Epub 2012 Dec 28.

The paradoxical effects of TNF inhibitors on bone mineral density and radiographic progression in patients with ankylosing spondylitis.

Kang KY[1], Ju JH, Park SH, Kim HY.

Arthritis Rheum. 2008 Oct;58(10):3063-70. doi: 10.1002/art.23901.

Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis.

van der Heijde D[1], Landewé R, Baraliakos X, Houben H, van Tubergen A, Williamson P, Xu W, Baker D, Goldstein N, Braun J; Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group.

Ann Rheum Dis. 2013 May 3. [Epub ahead of print]

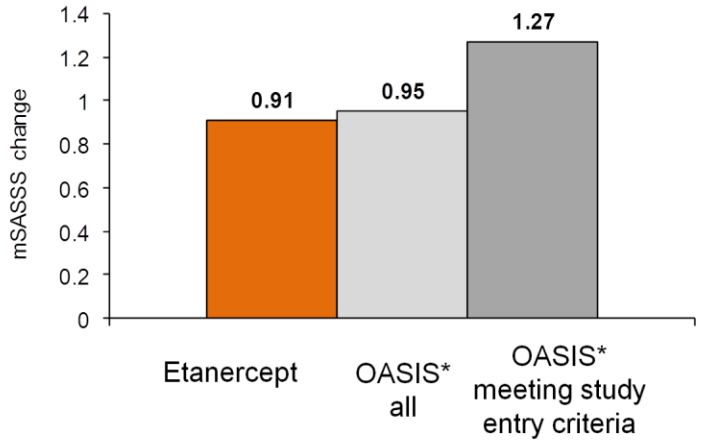
The effect of two golimumab doses on radiographic progression in ankylosing spondylitis: results through 4 years of the GO-RAISE trial.

Braun J[1], Baraliakos X, Hermann KG, Deodhar A, van der Heijde D, Inman R, Beutler A, Zhou Y, Xu S, Hsu B.

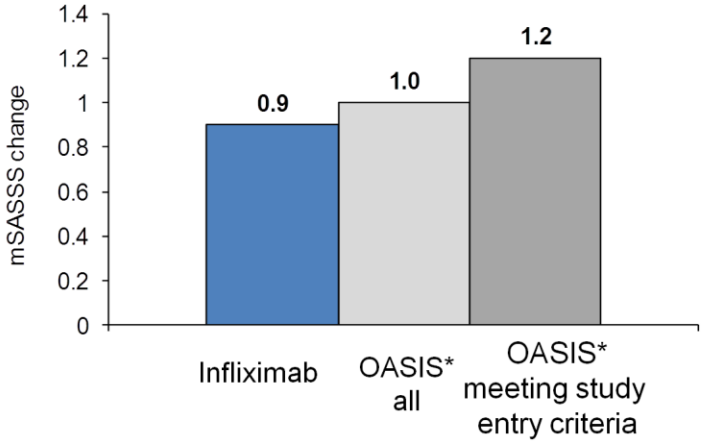
- Results not consistent and well designed prospective studies done independently are lacking so the case for prevention has not been made

Anti-TNFα-Therapy over 2 Years Does not Inhibit Radiographic Progression in AS

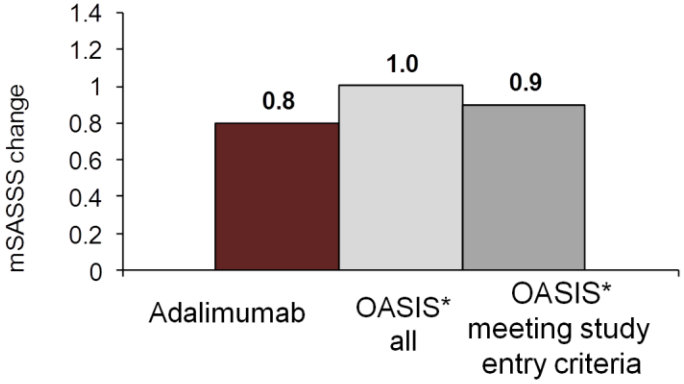
Etanercept[1]



Infliximab[2]



Adalimumab[3]



*OASIS=historical AS control group without anti-TNF therapy over 2 years
All comparisons p-value NS.

1. van der Heijde D et al. Arthritis Rheum 2008;58:1324-31
2. van der Heijde D et al. Arthritis Rheum 2008;58:3063-70
3. van der Heijde D et al. Arthritis Res Ther 2009;11:R127

Other aspects of Anti-TNFα treatment in AS - summary

- Therapy is effective in (the ASAS 2009 definition of) Axial SpA;
- Treatment is safe long-term;
- Switching is a valid strategy for inefficacy on one agent;
- Remission following withdrawal of treatment does occur in some patients though predictors of remission are not known.

Biologics other than TNF α Inhibitors and Small Molecules for AS Treatment

Target	Targeting substance	Efficacy in AS
B-cells	Rituximab (monoclonal antibody to CD20)	+/-
T-cells	Abatacept (inhibitor of T-cell co-stimulation)	-
Interleukin-1	Anakinra (IL-1 receptor antagonist)	-
Interleukin-6	Tocilizumab (monoclonal antibody to IL-6 receptor)	-
	Sarilumab (monoclonal antibody to IL-6 receptor)	-
Interleukin-17	Secukinumab (monoclonal antibody to IL-17)	+
	Ixekizumab (monoclonal antibody to IL-17)	?
Interleukin-12/23	Ustekinumab (monoclonal antibody to p-40-chain IL-12/23)	+/-
	Briakinumab (monoclonal antibody to p-40-chain IL-12/23)	?
Phosphodiesterase 4	Apremilast (PDE4 inhibitor, small molecule)	+/-
Janus kinase	Tofacitinib (JAK inhibitor, small molecule)	?

+ effective as shown in randomized controlled trials, +/- there are some data on a positive effect from pilot trials, - not effective, ? no data available regarding efficacy

Modified from: Song IH and Poddubnyy D. Curr Opin Rheumatol 2011;23:346-51

ASAS

Management of AS-aSpA Overview

- Exercise
  - Can slow progression of spinal stiffness
  - Can address fatigue – poorly studied
- Education
  - About enthesitis; back care; exercise, NSAID use; occupational aspects; coping with fatigue
- NSAIDs
  - Reduce IBP and almost certainly don't reduce bone changes
- Injection of steroids for enthesitis
  - Are useful for certain patients and may spare the use of DMARDs
- DMARDs
  - None have proved effective for spinal disease but are used for significant peripheral joint and/or enthesis disease
- Surgery
  - Rarely done but spinal osteotomy can correct severe kyphosis
- Anti-TNFα
  - All are effective for spinal and peripheral symptoms
  - ?variable / ? Lesser response of enthesitis

Il-17 pathway blocking – efficacy unknown

Psoriatic arthritis - patterns

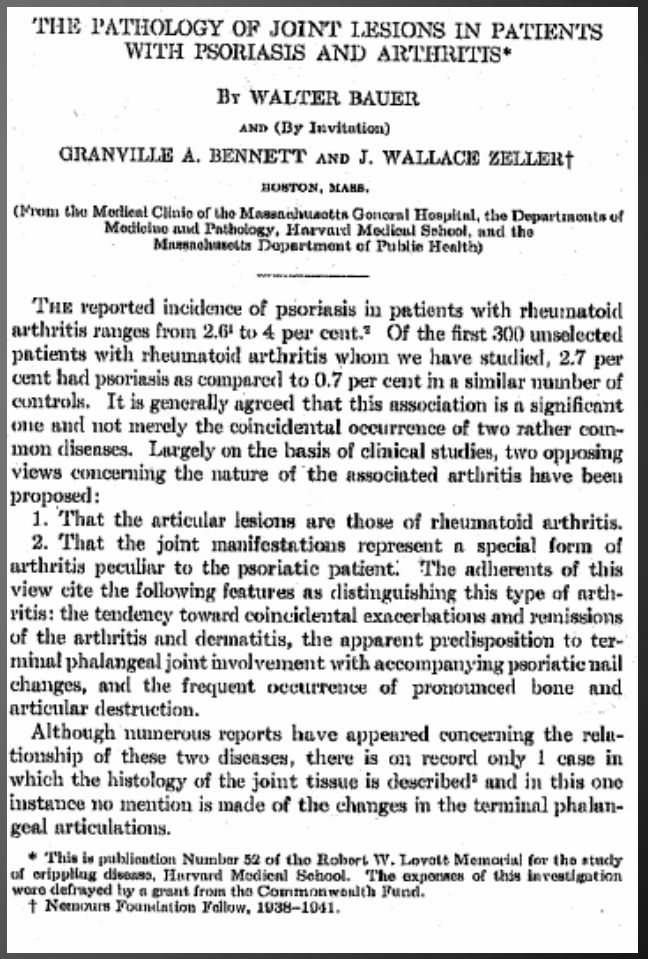
- Asymmetric oligoarticular pattern +/- spondylitis;
- Polyarticular pattern;
- DIPJ pattern with nail changes
- Arthritis mutilans (digit 'telescoping');
- Enthesopathy;
- Psoriatic arthritis-sine-psoriasis;

Patterns/features not exclusive simultaneously nor over time
Clinical patterns don't segregate with genotypes

MSK lesions include: entheses, bone, synovium, tendon

Fatigue – v common

Ps-disease may include skin, MSK and gut manifestations



THE PATHOLOGY OF JOINT LESIONS IN PATIENTS WITH PSORIASIS AND ARTHRITIS*

By WALTER BAUER

and (By Invitation)

GRANVILLE A. BENNETT and J. WALLACE ZELLER†

BOSTON, MASS.

(From the Medical Clinic of the Massachusetts General Hospital, the Departments of Medicine and Pathology, Harvard Medical School, and the Massachusetts Department of Public Health)

THE reported incidence of psoriasis in patients with rheumatoid arthritis ranges from 2.6[1] to 4 per cent.[2] Of the first 300 unselected patients with rheumatoid arthritis whom we have studied, 2.7 per cent had psoriasis as compared to 0.7 per cent in a similar number of controls. It is generally agreed that this association is a significant one and not merely the coincidental occurrence of two rather common diseases. Largely on the basis of clinical studies, two opposing views concerning the nature of the associated arthritis have been proposed:

1. That the articular lesions are those of rheumatoid arthritis.
2. That the joint manifestations represent a special form of arthritis peculiar to the psoriatic patient. The adherents of this view cite the following features as distinguishing this type of arthritis: the tendency toward coincidental exacerbations and remissions of the arthritis and dermatitis, the apparent predisposition to terminal phalangeal joint involvement with accompanying psoriatic nail changes, and the frequent occurrence of pronounced bone and articular destruction.

Although numerous reports have appeared concerning the relationship of these two diseases, there is on record only 1 case in which the histology of the joint tissue is described[3] and in this one instance no mention is made of the changes in the terminal phalangeal articulations.

* This is publication Number 52 of the Robert W. Lovett Memorial for the study of crippling disease, Harvard Medical School. The expenses of this investigation were defrayed by a grant from the Commonwealth Fund.

† Nemours Foundation Fellow, 1938–1941.

Ps immunogenetics

J Autoimmun. 2015 Jul 24. pii: S0896-8411(15)30011-1. doi: 10.1016/j.jaut.2015.07.008. [Epub ahead of print]

The immunogenetics of Psoriasis: A comprehensive review.

Harden JL[1], Krueger JG[2], Bowcock AM[3].

⊕ Author information

Abstract

Psoriasis vulgaris is a common, chronic inflammatory skin disease with a complex etiology involving genetic risk factors and environmental triggers. Here we describe the many known genetic predispositions of psoriasis with respect to immune genes and their encoded pathways in psoriasis susceptibility. These genes span an array of functions that involve antigen presentation (HLA-Cw6, ERAP1, ERAP2, MICA), the IL-23 axis (IL12Bp40, IL23Ap19, IL23R, JAK2, TYK2), T-cell development and T-cells polarization (RUNX1, RUNX3, STAT3, TAGAP, IL4, IL13), innate immunity (CARD14, c-REL, TRAF3IP2, DDX58, IFIH1), and negative regulators of immune responses (TNIP1, TNFAIP3, NFKBIA, ZC3H12C, IL36RN, SOCS1). The contribution of some of these gene products to psoriatic disease has also been revealed in recent years through targeting of key immune components, such as the Th17/IL-23 axis which has been highly successful in disease treatment. However, many of the genetic findings involve immune genes with less clear roles in psoriasis pathogenesis. This is particularly the case for those genes involved in innate immunity and negative regulation of immune specific pathways. It is possible that risk alleles of these genes decrease the threshold for the initial activation of the innate immune response. This could then lead to the onslaught of the pathogenic adaptive immune response known to be active in psoriatic skin. However, precisely how these various genes affect immunobiology need to be determined and some are speculated upon in this review. These novel genetic findings also open opportunities to explore novel therapeutic targets and potentially the development of personalized medicine, as well as discover new biology of human skin disease.

PsA PATHOPHYSIOLOGY

- **Genetics**
  - Association with MHC class I alleles, IL-1 cluster, TNF, IL-23R, and IL-12
  - IL-23R and HLA CW-6 have stronger links to PsA
  - MICA - A methionine/valine polymorphism at amino acid 129 of the major histocompatibility complex class I chain-related gene A (MICA-129) categorizes alleles into strong and weak binders of the natural killer (NK) and T-cell receptor NKG2D) stronger association with Ps vs PsA
- **Aberrant bone remodeling**
  - Overexpression of RANKL and increased levels of circulating OCP
  - Bone resorption triggered by TNFA
  - Increased pathologic bone formation linked to BMP expression and possibly the Wnt signaling pathway

J Clin Invest. 2003 Mar;111(6):821-31.

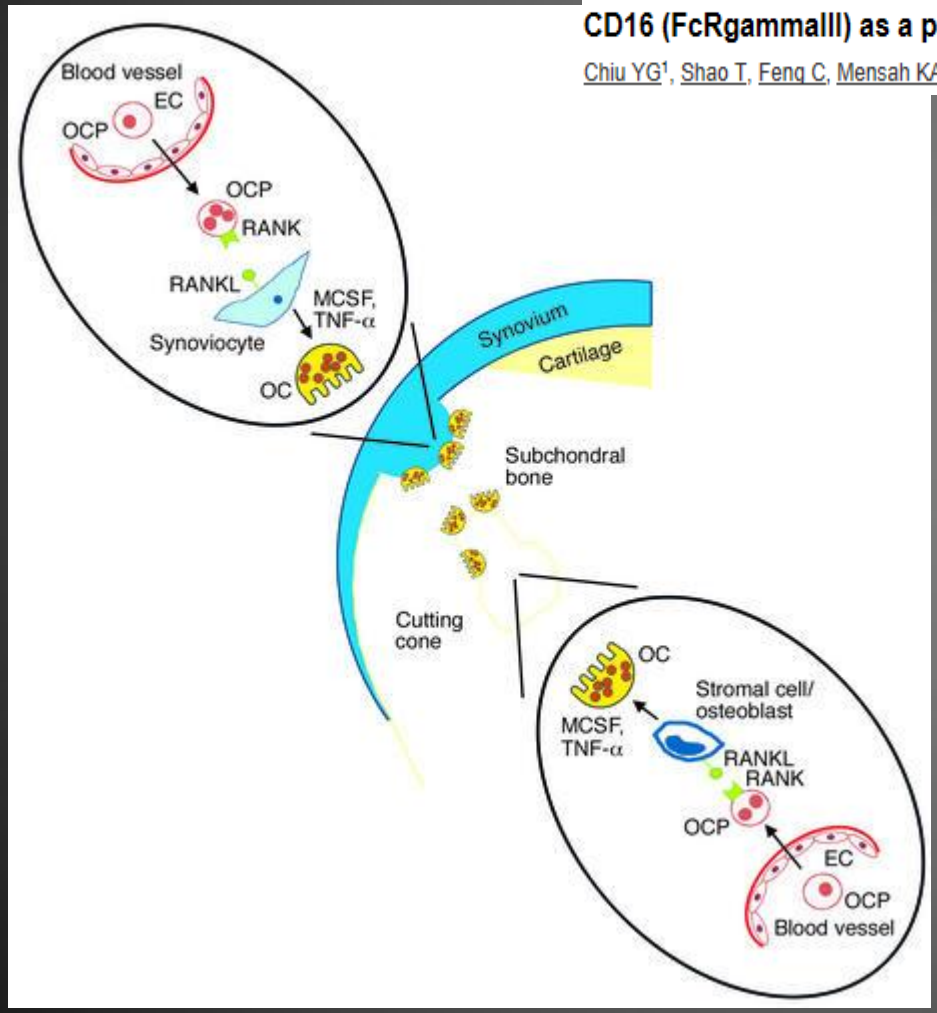
Mechanisms of TNF-alpha- and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis.

Ritchlin CT[1], Haas-Smith SA, Li P, Hicks DG, Schwarz EM.

Arthritis Res Ther. 2010;12(1):R14. doi: 10.1186/ar2915. Epub 2010 Jan 26.

CD16 (FcRgammaIII) as a potential marker of osteoclast precursors in psoriatic arthrit

Chiu YG[1], Shao T, Feng C, Mensah KA, Thullen M, Schwarz EM, Ritchlin CT.



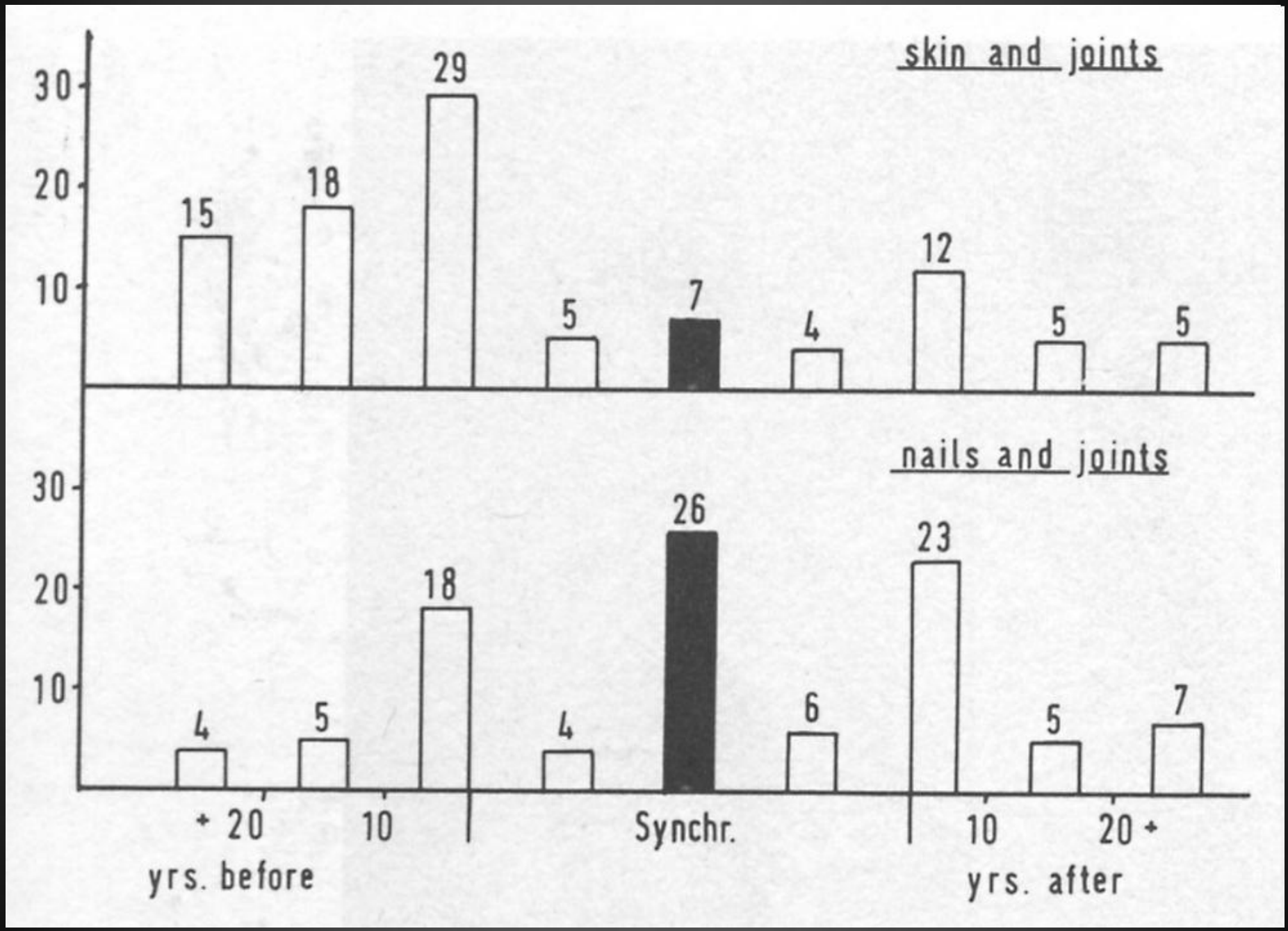
CASPAR criteria (Specificity 0.987, sensitivity 0.914)

Inflammatory articular disease (joint, spine, or entheseal)	
With 3 or more points from the following:	
1. Current psoriasis (scores 2 points)	*Psoriatic skin or scalp disease present today as judged by a rheumatologist*
2. Personal history of psoriasis (if current psoriasis not present)	*A history of psoriasis that may be obtained from patient, family doctor, dermatologist or rheumatologist*
3. Family history of psoriasis (if personal history of psoriasis or current psoriasis is not present)	*A history of psoriasis in a first or second degree relative according to patient report*
4. Psoriatic nail dystrophy	*Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination*
5. A negative test for rheumatoid factor	*By any method except latex but preferably by ELISA or nephlemetry, according to the local laboratory reference range*
6. Current dactylitis	*Swelling of an entire digit*
7. History of dactylitis (if current dactylitis is not present)	*A history of dactylitis recorded by a rheumatologist*
8. 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*

Genetics

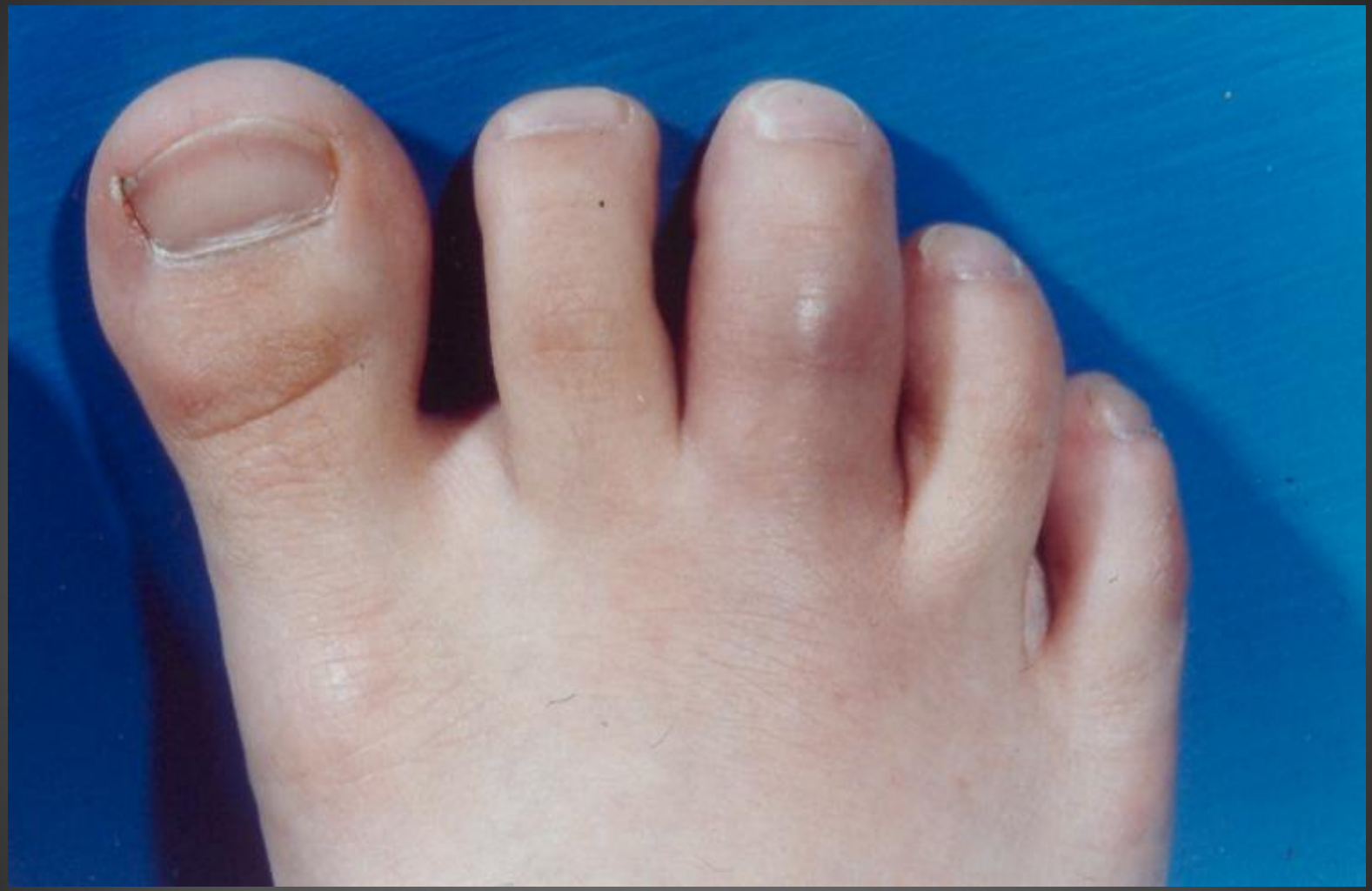
Strong linkage familial linkage

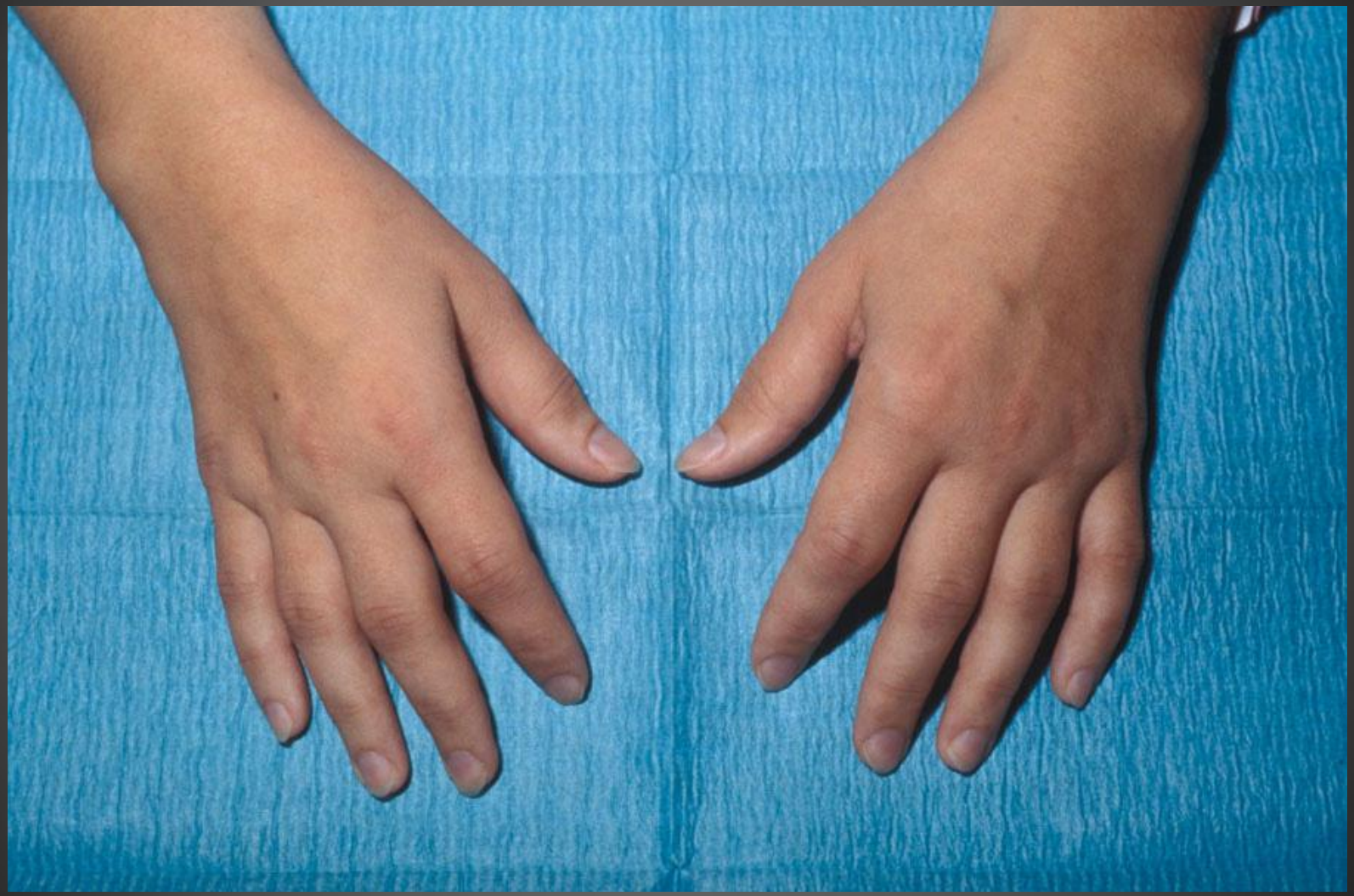
Susceptibility/disease expression loci: 16-25; many at 6p; most are IR-related

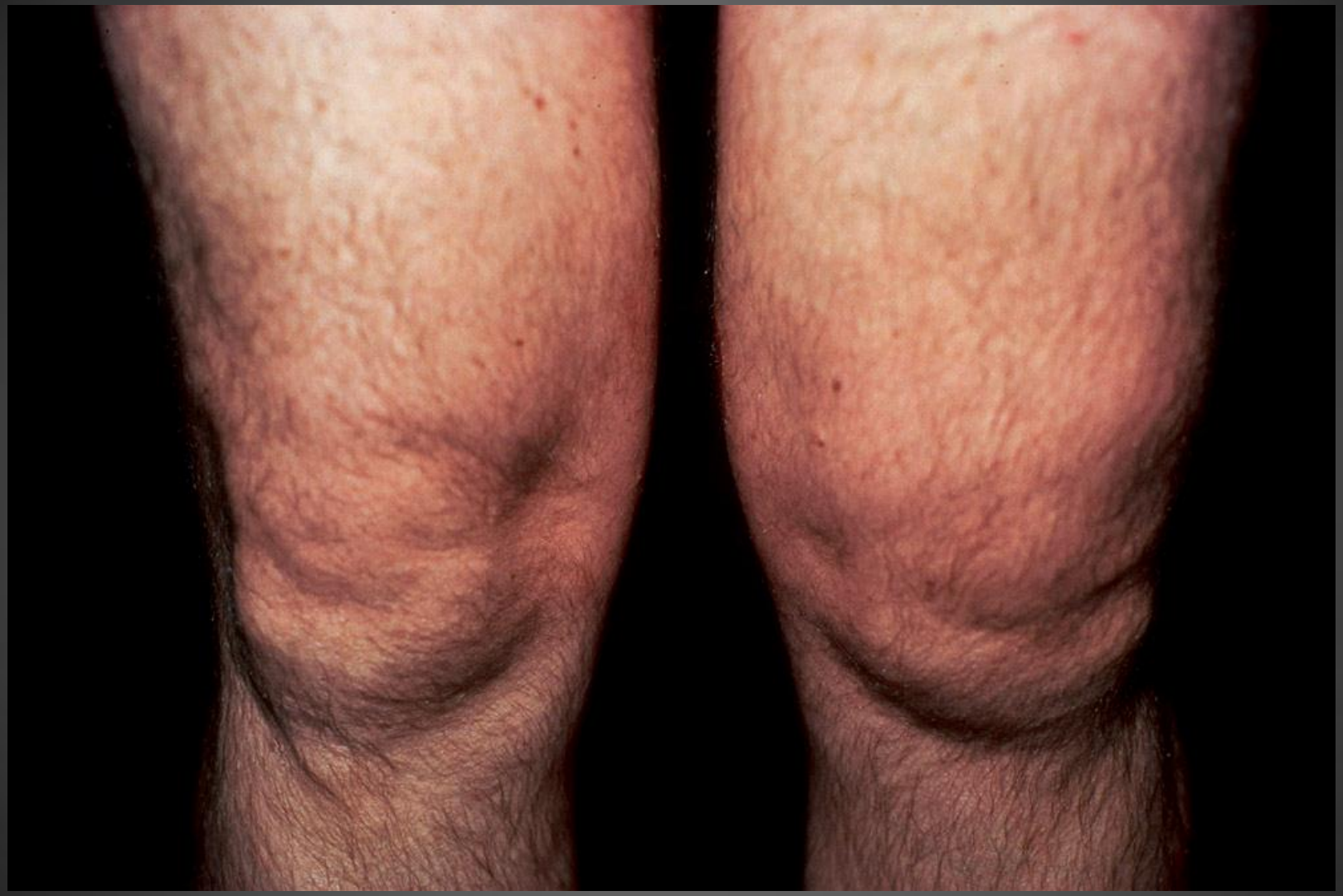

skin and joints
30
20
10
15
18
29
5
7
4
12
5
5
nails and joints
30
20
10
4
5
18
4
26
6
23
5
7
+ 20
10
Synchr.
10
20 +
yrs. before
yrs. after

Psoriatic arthritis - lesions

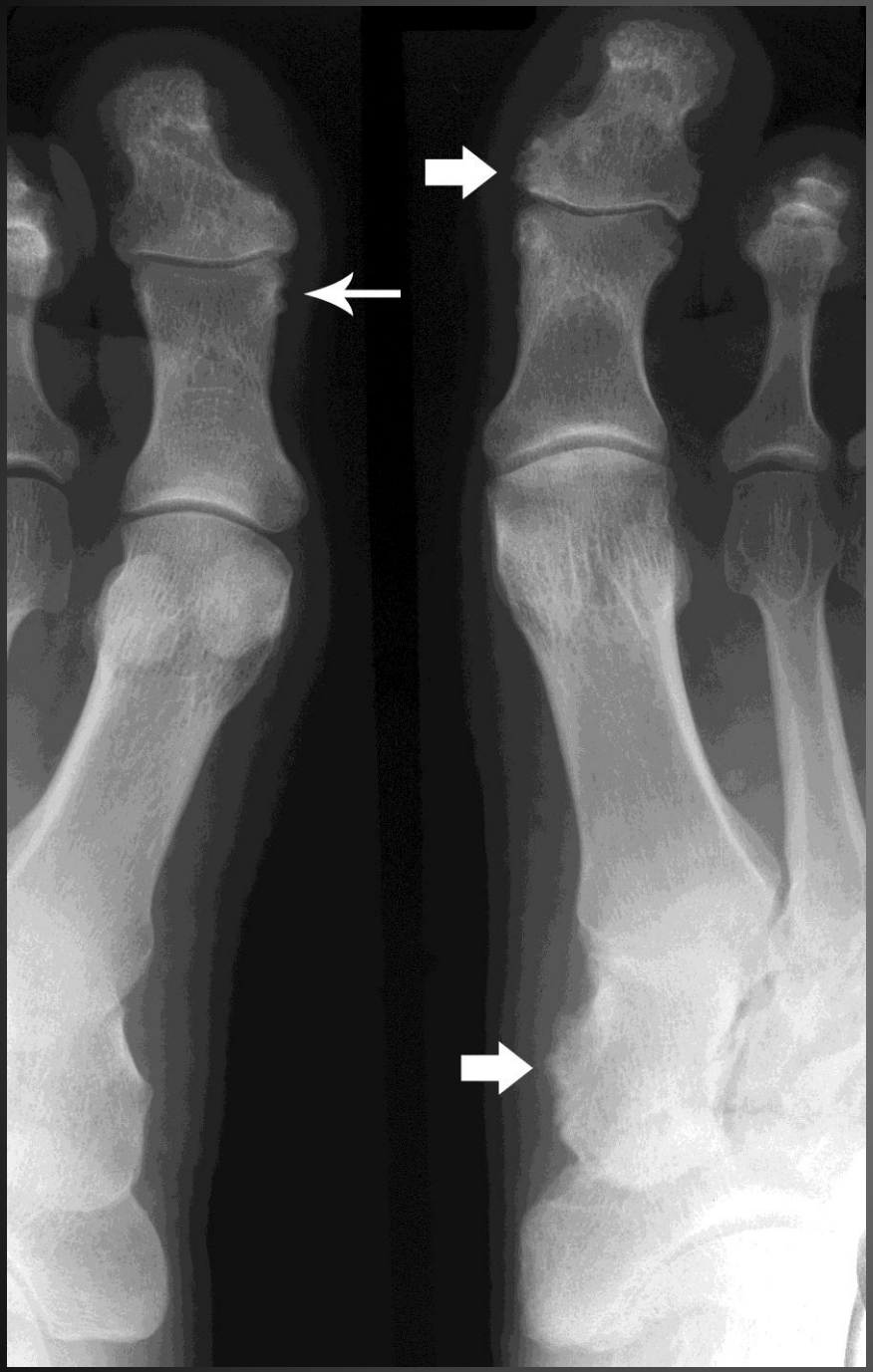
- Periosteal
  - New bone – syndesmophytes, enthesophytes, juxta-articular periosteal apposition
- Discitis
- Dactylitis
- Synovitis
- Enthesitis
  - Plantar fasciitis
  - Insertional Achilles Pain
  - Deltoid origin
  - Sacroiliitis and ileal rim enthesitis
  - Humeral epicondylitis and greater trochanter pain
  - Symphysitis

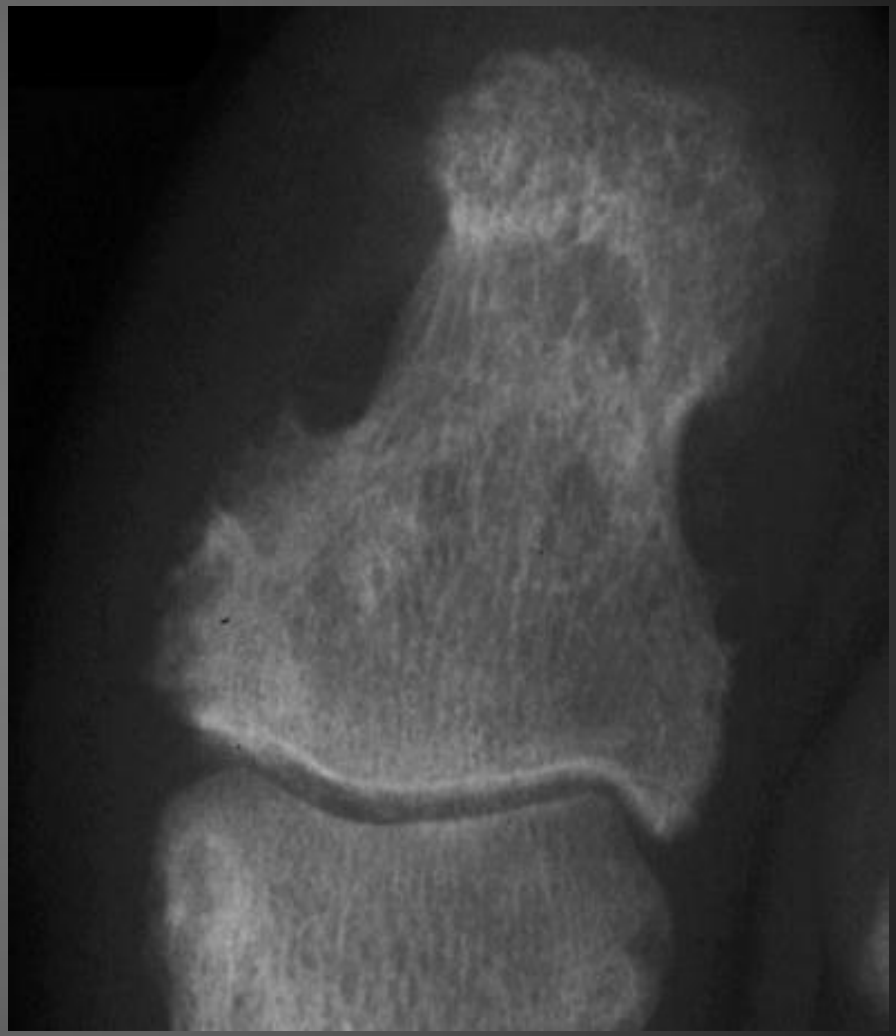


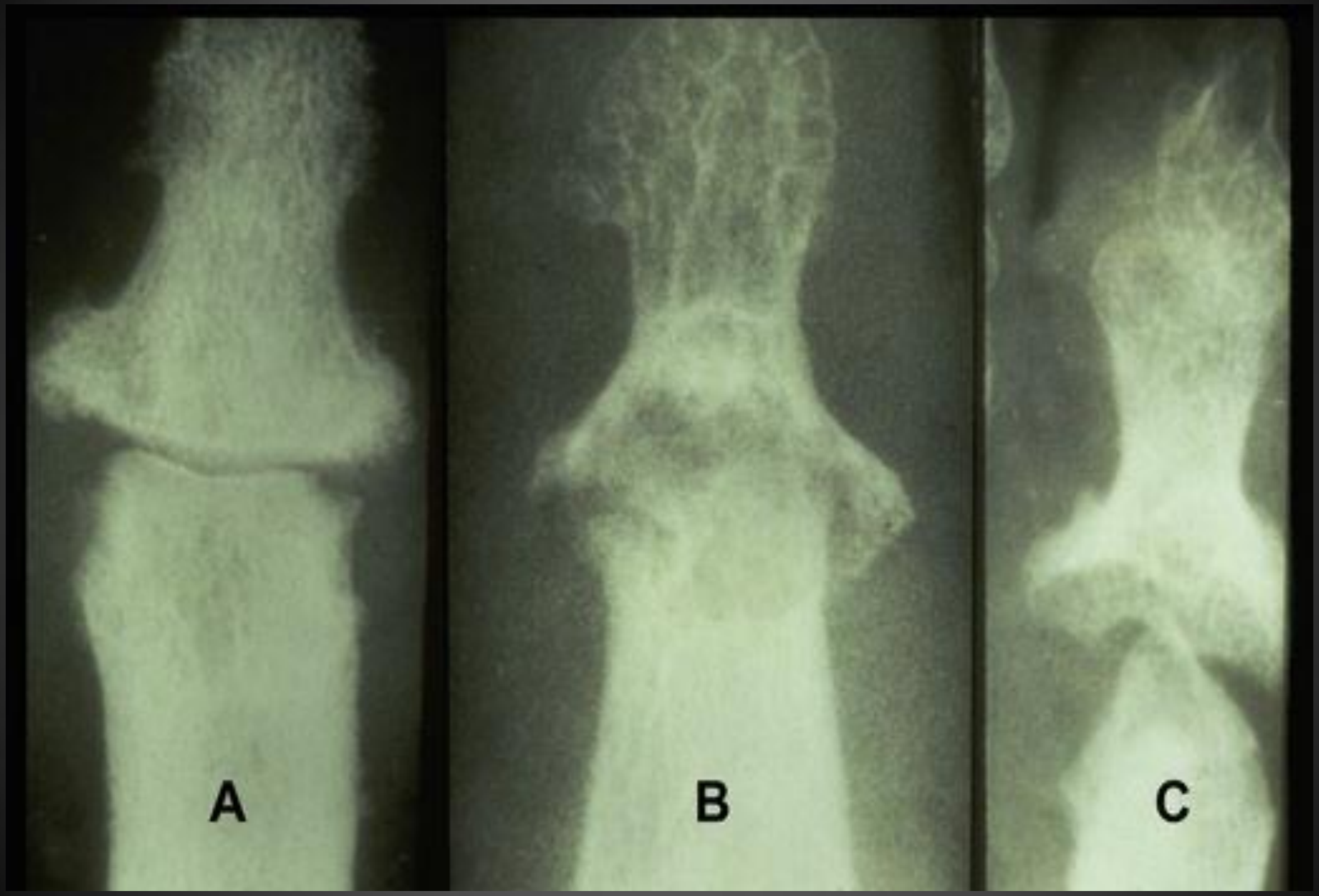


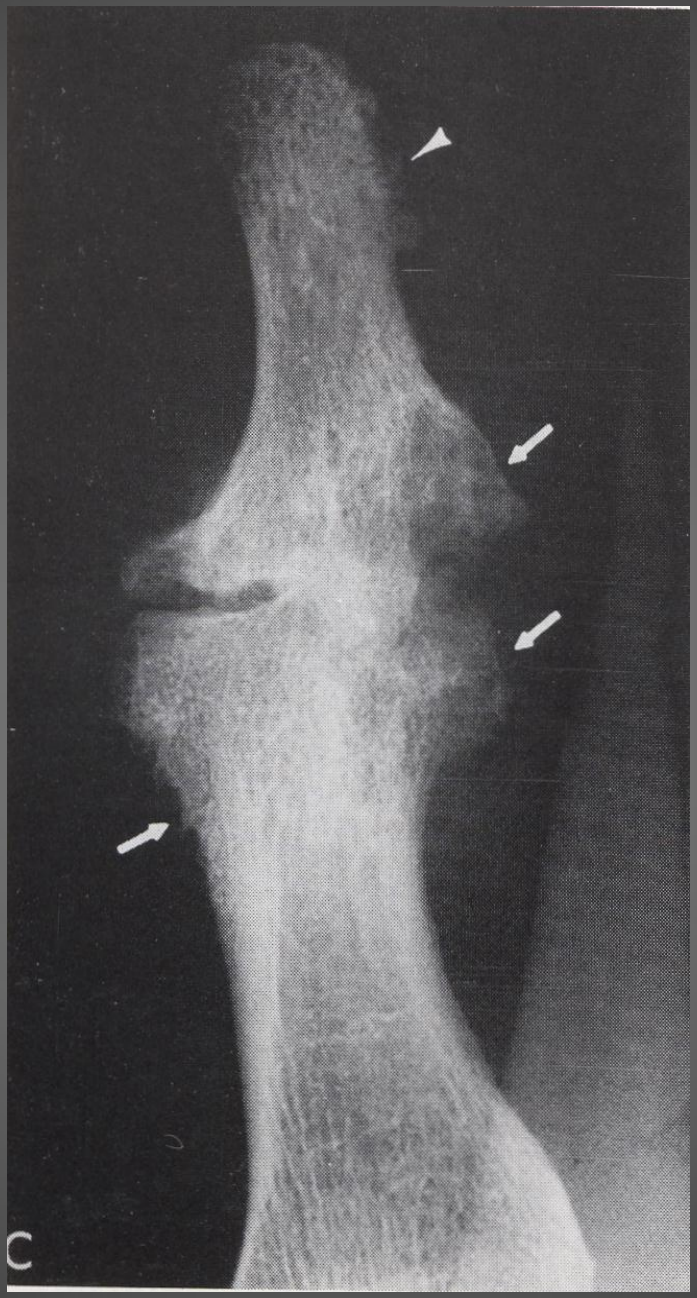


Knee synovitis in SpAs often associated with large volume effusions and thick synovial lining, often asymmetrical






A
B
C


C

PsA therapeutics

- NSAIDs
- DMARDs therapy efficacy data is available but not high grade evidence for SZP, MTX, CYA
- Reasonable evidence is available for LEFLUNOMIDE (Arava)

Arthritis Rheum. 2004 Jun;50(6):1939-50.

Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial.

Kaltwasser JP[1], Nash P, Gladman D, Rosen CF, Behrens F, Jones P, Wollenhaupt J, Falk FG, Mease P; Treatment of Psoriatic Arthritis Study Group.

Rheumatology (Oxford). 2012 Aug;51(8):1368-77. doi: 10.1093/rheumatology/kes001. Epub 2012 Feb 17.

A randomized placebo-controlled trial of methotrexate in psoriatic arthritis.

Kingsley GH[1], Kowalczyk A, Taylor H, Ibrahim F, Packham JC, McHugh NJ, Mulherin DM, Kitas GD, Chakravarty K, Tom BD, O'Keeffe AG, Maddison PJ, Scott DL.

Author information

Abstract

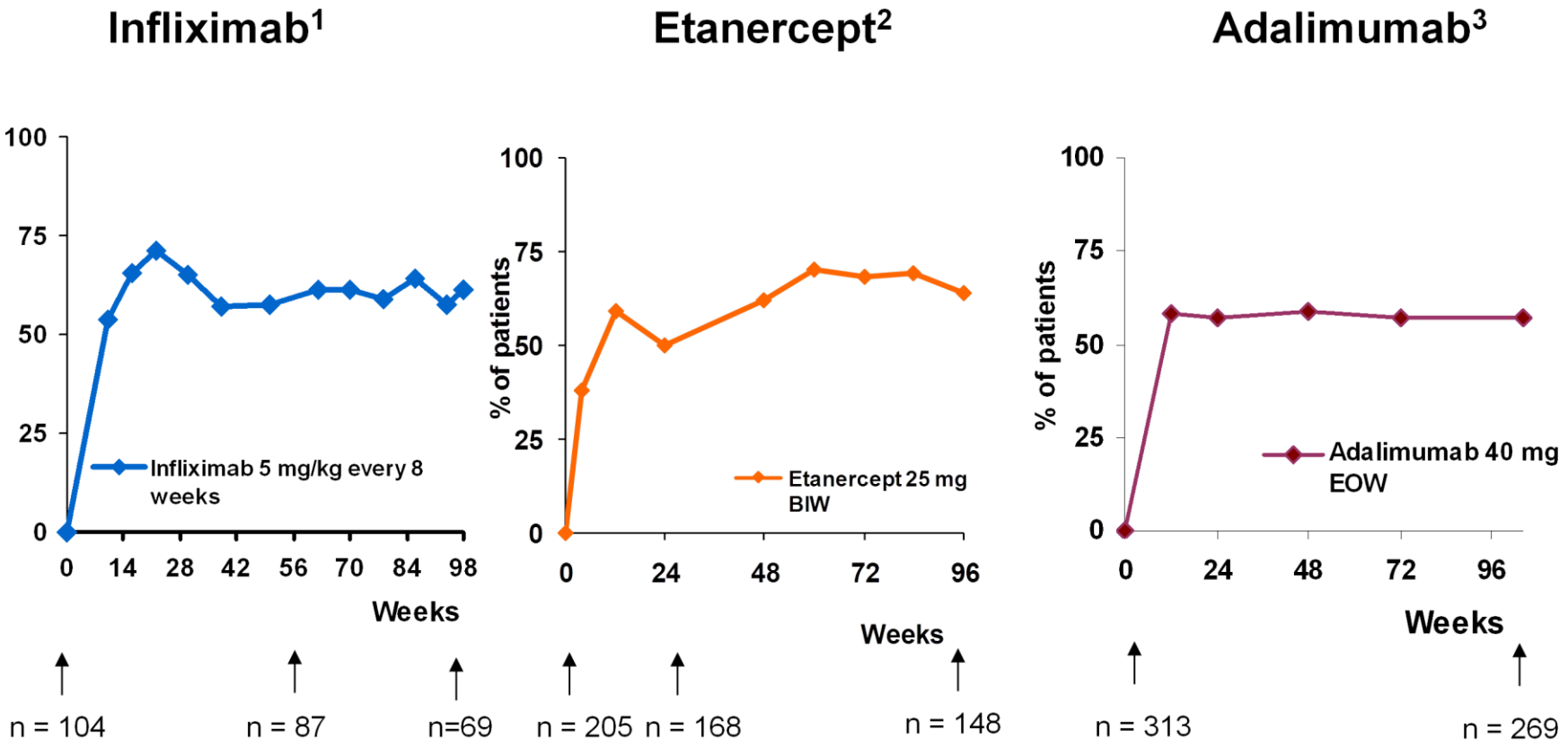
OBJECTIVE: MTX is widely used to treat synovitis in PsA without supporting trial evidence. The aim of our study was to test the value of MTX in the first large randomized placebo-controlled trial (RCT) in PsA.

METHODS: A 6-month double-blind RCT compared MTX (15 mg/week) with placebo in active PsA. The primary outcome was PsA response criteria (PsARC). Other outcomes included ACR20, DAS-28 and their individual components. Missing data were imputed using multiple imputation methods. Treatments were compared using logistic regression analysis (adjusted for age, sex, disease duration and, where appropriate, individual baseline scores).

RESULTS: Four hundred and sixty-two patients were screened and 221 recruited. One hundred and nine patients received MTX and 112 received placebo. Forty-four patients were lost to follow-up (21 MTX, 23 placebo). Twenty-six patients discontinued treatment (14 MTX, 12 placebo). Comparing MTX with placebo in all randomized patients at 6 months showed no significant effect on PsARC [odds ratio (OR) 1.77, 95% CI 0.97, 3.23], ACR20 (OR 2.00, 95% CI 0.65, 6.22) or DAS-28 (OR 1.70, 95% CI 0.90, 3.17). There were also no significant treatment effects on tender and swollen joint counts, ESR, CRP, HAQ and pain. The only benefits of MTX were reductions in patient and assessor global scores and skin scores at 6 months ($P = 0.03$, $P < 0.001$ and $P = 0.02$, respectively). There were no unexpected adverse events.

CONCLUSIONS: This trial of active PsA found no evidence for MTX improving synovitis and consequently raises questions about its classification as a disease-modifying drug in PsA. Trial registration. Current Controlled Trials, www.controlled-trials.com, ISRCTN:54376151.

Long Term Efficacy of TNF-Antagonists for the Treatment of Psoriatric Arthritis (ACR 20)



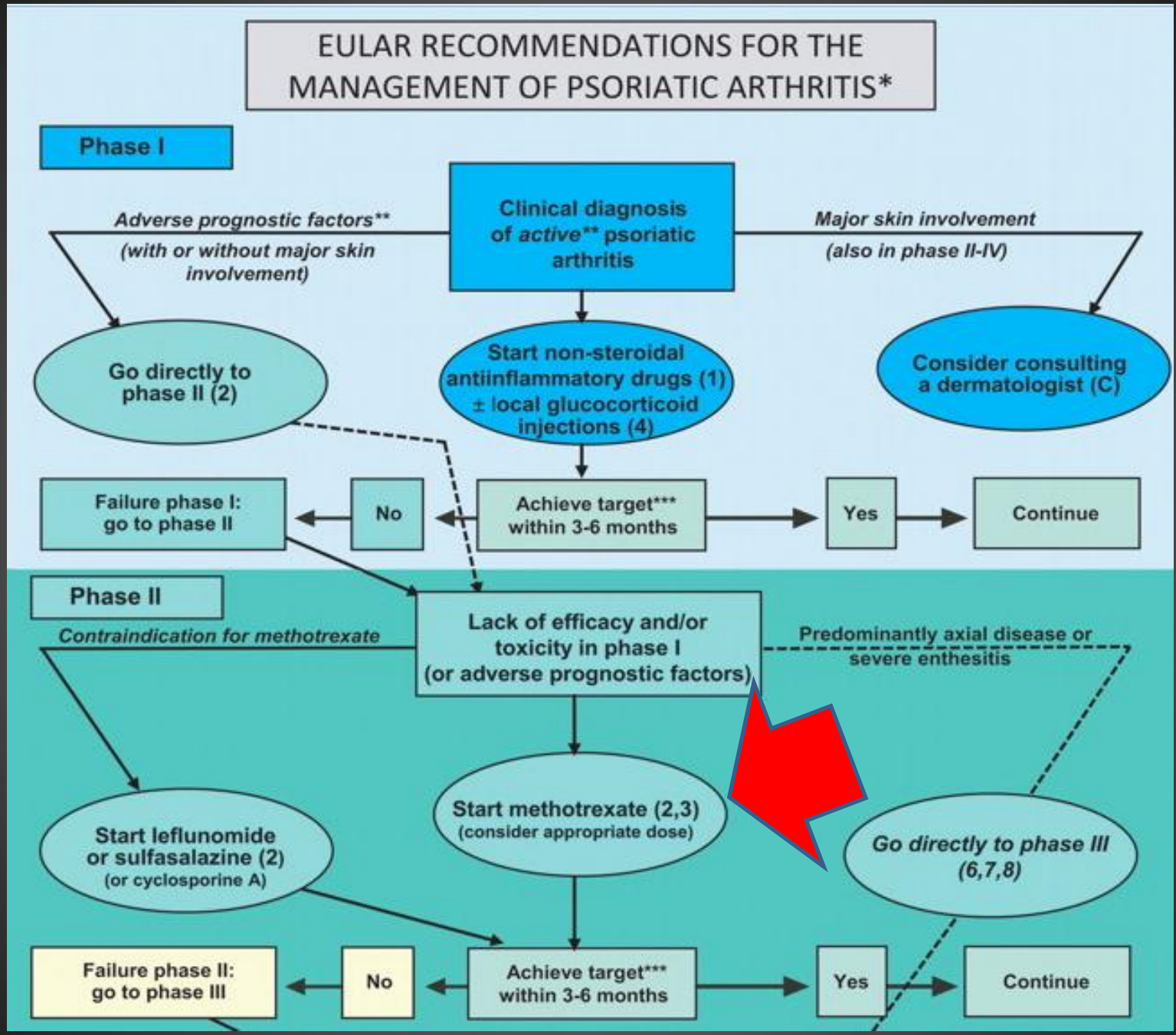
1. Antoni CE et al. J Rheumatol 2008;35:869-76
2. Mease P et al. J Rheumatol 2006;33:712-21
3. Mease PJ et al. Ann Rheum Dis 2009;68:702-9

Dosage of TNFα-Blockers in AS, PsA and IBD

Drug	Dosage AS	Dosage PsA	Dosage IBD	Application
Infliximab	5 mg/kg	5 mg/kg	5 mg/kg	i.v. at week 0, 2, 6, q6 / q8*
Etanercept	25 mg 50 mg	25 mg 50 mg	Not used	s.c. twice weekly s.c. once weekly
Adalimumab	40 mg	40 mg	40 mg	s.c. every 2 weeks**
Golimumab	50 mg	50 mg	Not used	s.c. every 4 weeks

* Psoriatic arthritis and inflammatory bowel disease (IBD)

** For IBD: initially higher dose


EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF PSORIATIC ARTHRITIS*
Phase I
Clinical diagnosis of active** psoriatic arthritis
Adverse prognostic factors**
(with or without major skin involvement)
Major skin involvement
(also in phase II-IV)
Go directly to phase II (2)
Start non-steroidal antiinflammatory drugs (1) ± local glucocorticoid injections (4)
Consider consulting a dermatologist (C)
Failure phase I: go to phase II
No
Achieve target*** within 3-6 months
Yes
Continue
Phase II
Contraindication for methotrexate
Lack of efficacy and/or toxicity in phase I (or adverse prognostic factors)
Predominantly axial disease or severe enthesitis
Start leflunomide or sulfasalazine (2)
(or cyclosporine A)
Start methotrexate (2,3)
(consider appropriate dose)
Go directly to phase III (6,7,8)
Failure phase II: go to phase III
No
Achieve target*** within 3-6 months
Yes
Continue

PsA therapeutics: Biologics – what do we know?

- There are robust data for all anti-TNFα therapies for improving signs and symptoms of PsA;
- There is evidence for prevention of joint damage as early as 26 weeks

Ann Rheum Dis. 2014 Feb 1;73(2):414-9. doi: 10.1136/annrheumdis-2012-202641. Epub 2013 Jan 25.

Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials.

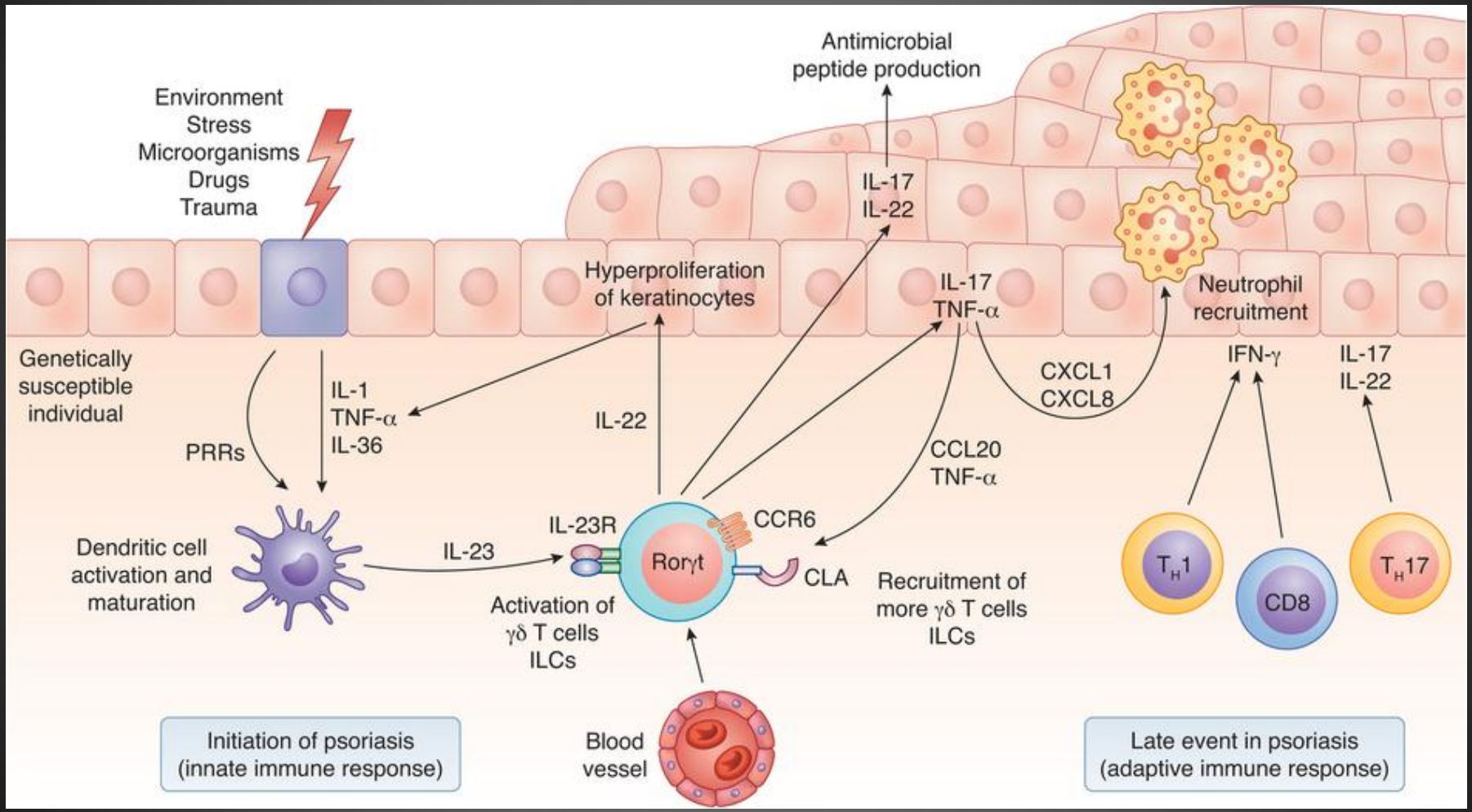
Goulabchand R[1], Mouterde G, Barnetche T, Lukas C, Morel J, Combe B.

- There is limited evidence for strategies for switching for inefficacy though some patients do benefit
- There is class effect in causing 'paradoxical Psoriasis'

PsA therapeutics: – what don't we know?

- Do combination therapies have benefit over monotherapy?
- Do DMARDs and/or anti-TNFα therapy reliably suppress enthesis-predominant disease?
- Can DMARDs be withdrawn and patients remain in remission? Whom?
- Do we have reliable, validated and clinically relevant clinical outcome measures (eg inflammation markers, fatigue, imaging)?
- Does anti-TNFα switch on processes which may aggravate/cause Psoriasis and enthesitis?

Immunopathogenesis of psoriasis



Nat Med. 2012 Jul 1;18(7):1069-76. doi: 10.1038/nm.2817.

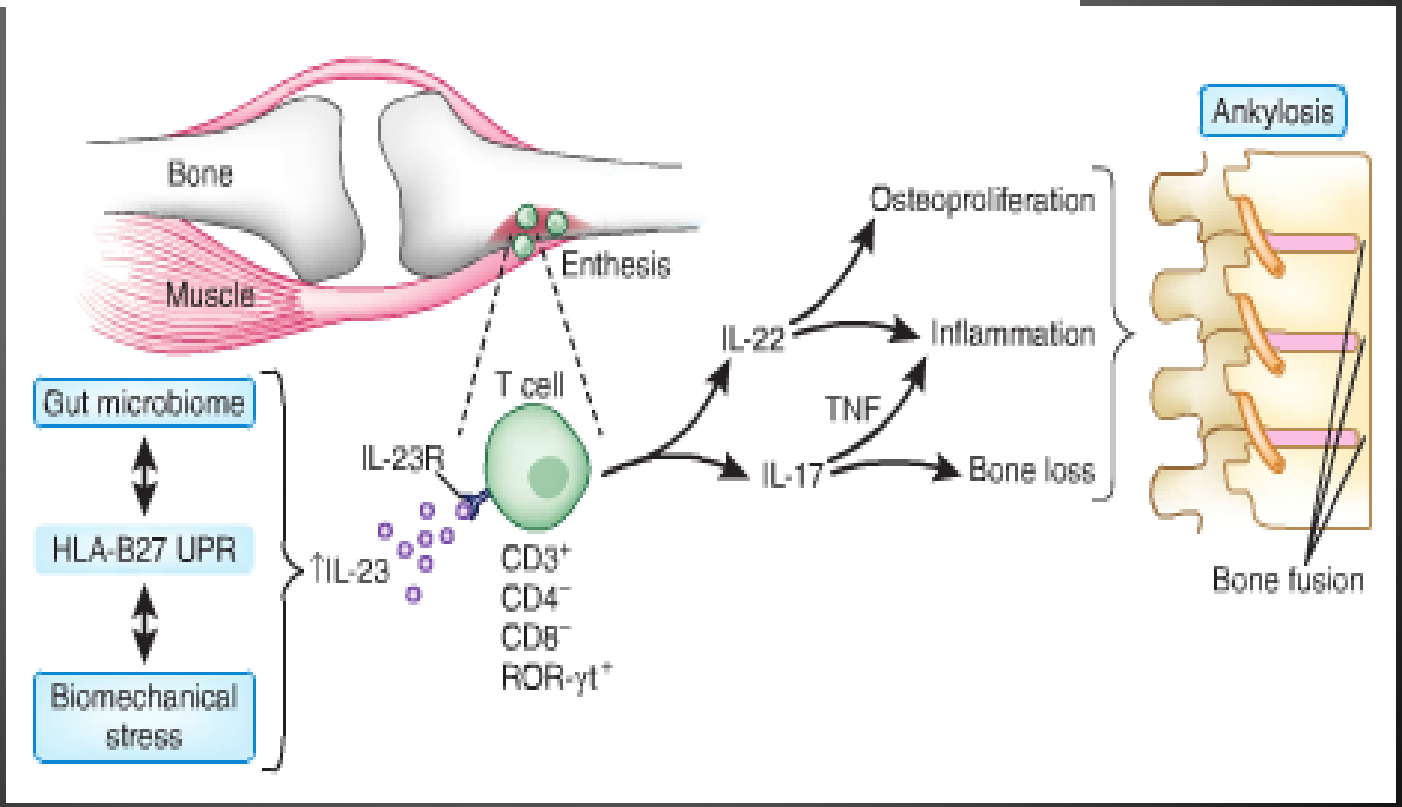
IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4-CD8- entheseal resident T cells.

Sherlock JP[1], Joyce-Shaikh B, Turner SP, Chao CC, Sathe M, Grein J, Gorman DM, Bowman EP, McClanahan TK, Yearley JH, Eberl G, Buckley CD, Kastelein RA, Pierce RH, Laface DM, Cua DJ.

⊕ Author information

Abstract

The spondyloarthropathies are a group of rheumatic diseases that are associated with inflammation at anatomically distal sites, particularly the tendon-bone attachments (entheses) and the aortic root. Serum concentrations of interleukin-23 (IL-23) are elevated and polymorphisms in the IL-23 receptor are associated with ankyosing spondylitis, however, it remains unclear whether IL-23 acts locally at the enthesis or distally on circulating cell populations. We show here that IL-23 is essential in enthesitis and acts on previously unidentified IL-23 receptor (IL-23R)(+), RAR-related orphan receptor γt (ROR-γt)(+)CD3(+)CD4(-)CD8(-), stem cell antigen 1 (Sca1)(+) entheseal resident T cells. These cells allow entheses to respond to IL-23 in vitro-in the absence of further cellular recruitment--and to elaborate inflammatory mediators including IL-6, IL-17, IL-22 and chemokine (C-X-C motif) ligand 1 (CXCL1). Notably, the in vivo expression of IL-23 is sufficient to phenocopy the human disease, with the specific and characteristic development of enthesitis and entheseal new bone formation in the initial complete absence of synovitis. As in the human condition, inflammation also develops in vivo at the aortic root and valve, which are structurally similar to entheses. The presence of these entheseal resident cells and their production of IL-22, which activates signal transducer and activator of transcription 3 (STAT3)-dependent osteoblast-mediated bone remodeling, explains why dysregulation of IL-23 results in inflammation at this precise anatomical site.



Anti-Il17 and Il-23/12 therapies

- Advances mainly in Il-17 and Il-23/Il-12 as therapy targets.

Ann Rheum Dis. 2014 Feb 1;73(2):349-56. doi: 10.1136/annrheumdis-2012-202646. Epub 2013 Jan 29.

Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial.

McInnes IB[1], Sieper J, Braun J, Emery P, van der Heijde D, Isaacs JD, Dahmen G, Wollenhaupt J, Schulze-Koops H, Kogan J, Ma S, Schumacher MM, Bertolino AP, Hueber W, Tak PP.

Ann Rheum Dis. 2014 Feb 19. doi: 10.1136/annrheumdis-2013-204741. [Epub ahead of print]

Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials.

Kavanaugh A[1], Ritchlin C, Rahman P, Puig L, Gottlieb AB, Li S, Wang Y, Noonan L, Brodmerkel C, Song M, Mendelsohn AM, McInnes IB; on behalf of the PSUMMIT-1 and 2 Study Groups.

- Ustekinumab is licensed for use in PsA though not authorised in UK (£10-20k [37-74k BRL]; NICE Final Appraisal Determination, March 2013)

Table – Agents in the pipeline for psoriatic arthritis

Agent	Target	Mechanism
Tocilizumab	IL-6 receptor	IL-6 receptor blockade
Ustekinumab	p40 subunit of IL-12/23	Blocks IL-23/T_H17 pathway
Apremilast	PDE4	Blocks cytokines and immune response
Anti–IL-17 Ab (AIN457)	IL-17A	Blocks IL-17A actions
Anti–IL-22 Ab	IL-22	Inhibits cell proliferation
Tofacitinib	JAK	Suppresses cytokine signaling
Denosumab	RANKL	Inhibits bone resorption

IL, interleukin; T_H, helper T cell; PDE, phosphodiesterase; Ab, antibody; JAK, Janus kinase; RANKL, receptor activator of nuclear factor-κB ligand.

Reactive arthritis

- Triggered by specific gut or genito-urinary infections
- Joint symptoms appear 1-3 week later
- Most cases resolve quickly but a proportion evolve into chronic spondyloarthropathy (AS)

Shortlist of SpA ReA-associated bacteria

- Salmonella
- Campylobacter - jejuni and coli
- Yersinia - enterocolitica and pseudotb.
- Shigella - flexneri, sonnei, dysenteri, boydii
- Chlamydia - trachomatis and pneumoniae
- Clostridium difficile

Post-infectious arthritis

- Post viral arthritis e.g. Parvovirus
- Post streptococcal arthritis
  - rheumatic fever
  - arthritis alone
- Post *Neisseria* arthritis
- Lyme disease
- Whipple's disease

- none of these are spondyloarthropathies

Reiter's syndrome??

- Reiter not first to describe the syndrome
  - thought it was due to a spirochaete
- Questionable subsequent career

- Often used as synonymous with sexually acquired ReA, but originally an enteric ReA

Incidence

- Chlamydia ReA - 46/million [Oslo]
- Enteric orgs ReA - 50/million [Oslo]
- Shigella ReA - 1.3/million [Finland]
  - ? 30/million exposed
- Campylobacter ReA - 43/million [Finland]

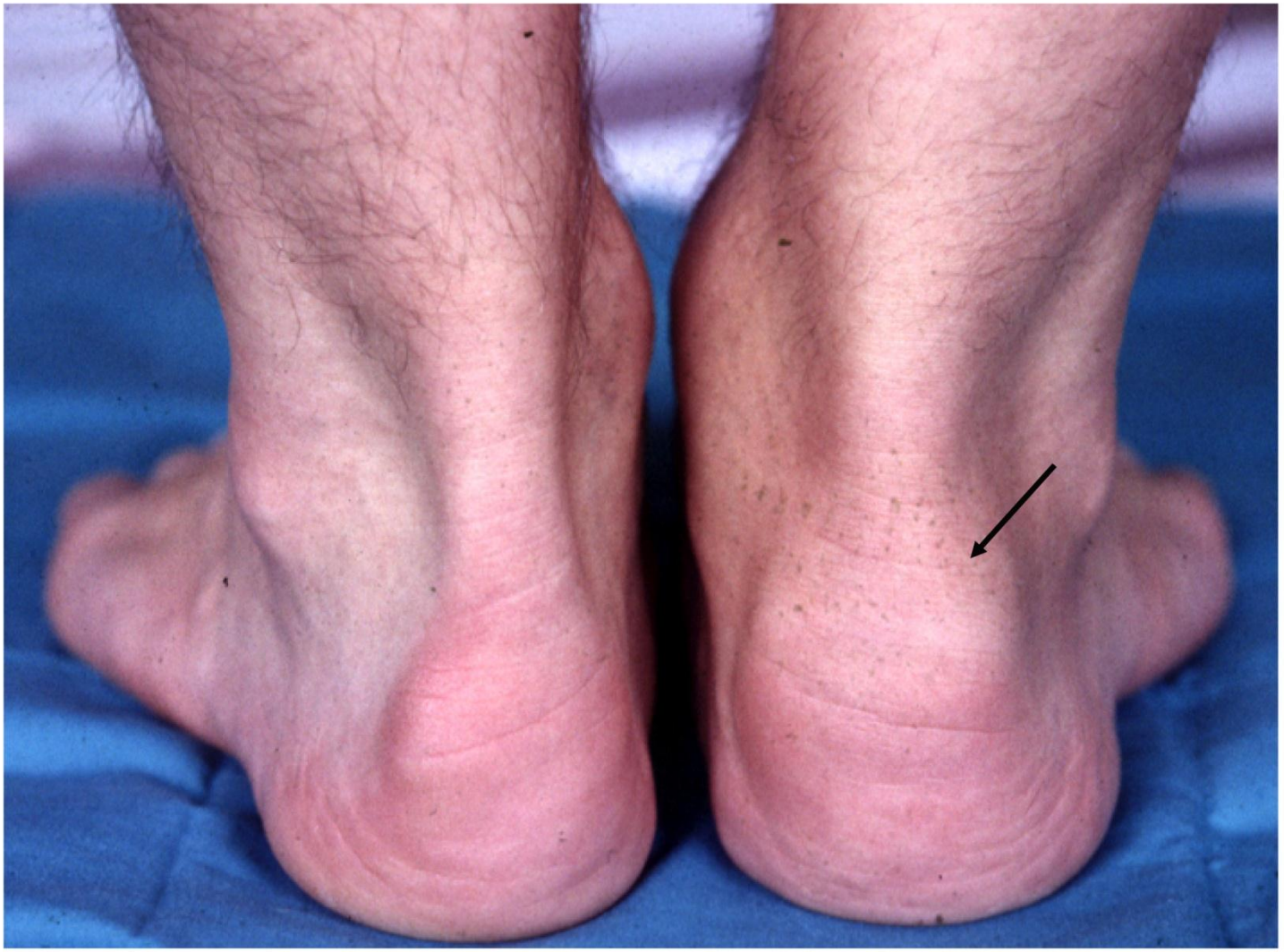
Forms of reactive arthritis

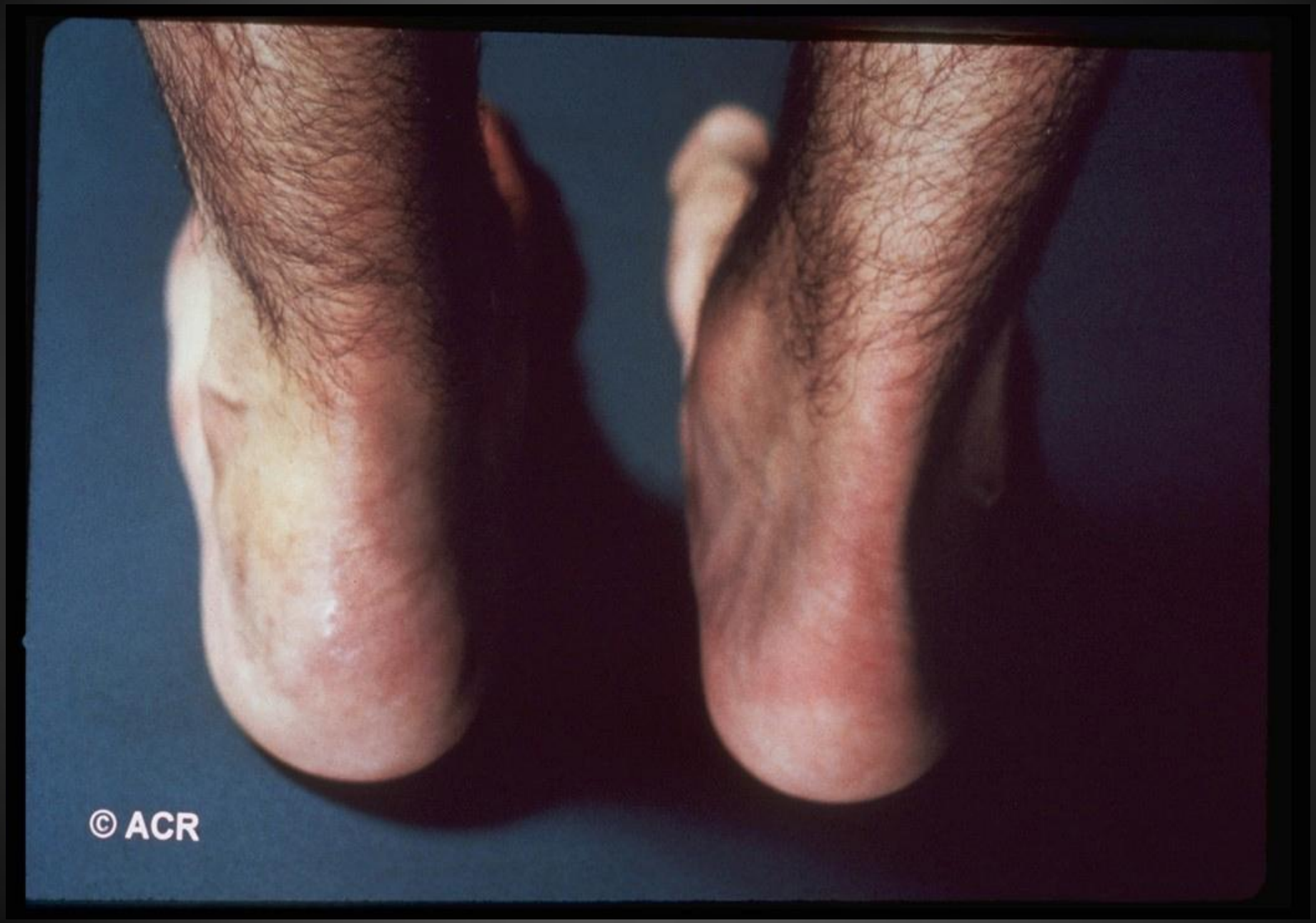
- "Rheumatologic" – presenting to secondary care
  - Inflammatory oligoarthritis + IBP involvement
- Milder disease – seen in primary care or non-presenting
  - Peripheral arthritis/enthesitis + back ache (IBP)
  - Self limiting

Clinical features for *early* Campylobacter-induced ReA

- 80% peripheral arthritis
  - 10% mono, 40% oligo, 50% poly
- 20% inflammatory back pain
- age 45 (20-74); 75% female; no children
- Onset 12 days (1-55)
- Duration: 50% 1 month; all <6months

Enthesitis (Insertion of Achilles Tendon at Calcaneus) Right Heel

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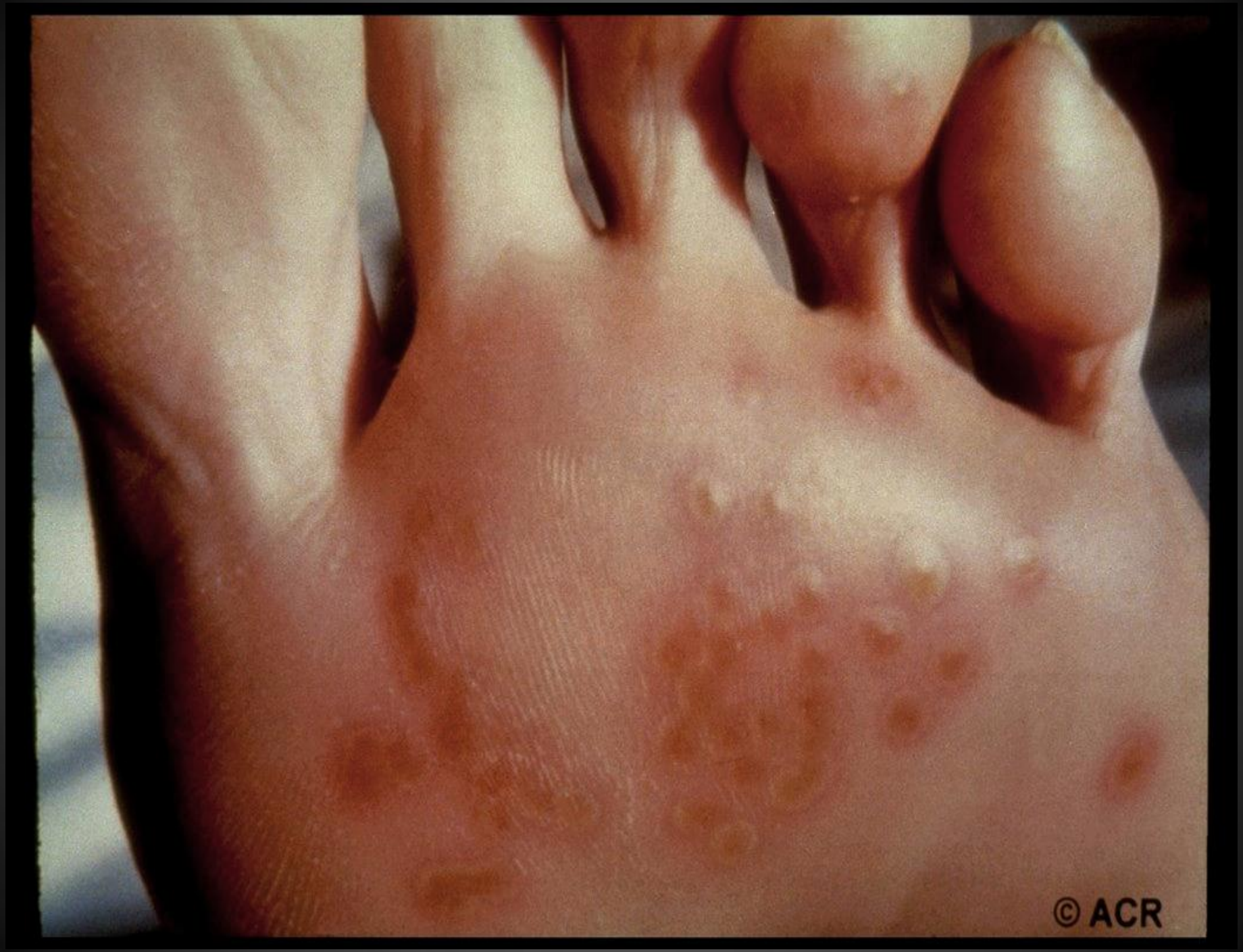
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ReA management

- Diagnosis
- Education, NSAIDs
- Steroids if acute and severe
- IA steroid if joint-focal (rule out infection and consider crystal arthritis if aspirating joint)
- Sulfasalazine for persistent disease though MTX also used;
- TNFi for recalcitrant cases ?PsA ?aSpA

Rationale for antibiotic therapy in ReA

- bacterial infection persists and bacteria/antigens reach the joint
- pro-inflammatory T cells recognize these antigens
- antibiotics should speed antigen clearance

Trial antibiotics Reactive arthritis: Ciprofloxacin: 3 months

- Asymmetric arthritis + enteritis/urethritis
- 36 active : 35 placebo; < 3 months disease
- 25% B27+; most enteric (54, 22 culture +ive; 3 CT)
- no difference in any 1^{o} endpoint ESR, joint count, global VAS, remission
- active group may be worse more i-a steroids (96 vs 62 injections)more DMARDs (8 vs 3) ~70% remission at 1 year

SpAs: summary

- SpAs are common (overall 2-3%; vs RA <1%)
- SpAs cause IBP and bone lesions
- B27 associated – variably depending on subclassification
- SpAs can relapse and remit through life and may be subtle in their effects
- PsA clearly a complicated disease clinically and in terms of genetic predisposition
- Respond to NSAIDs
- DMARDs not effective in spinal inflammatory disease all but only in peripheral disease
- Anti-TNFα effective in all and effective in treating axial and peripheral disease
- IL-23/Th17 axis blocking is a developing and key therapeutic area

Summary

- The classification of SpAs has evolved in recent years and has/will expand our ability to study and treat the wider SpA disease phenotype, and earlier;
- NSAIDs, DMARDs and Anti-TNF therapies, though effective for symptoms in AS/axial SpA have yet to show robust evidence for reducing spinal bone proliferation over time;
- Therapeutic studies have yet to show the most effective and cost efficient combinations of treatments in PsA, though the future is promising (with cheaper!) anti Il-23 and Il-17 biologics