

# Early Diagnosis and Management of Inflammatory Arthritis- A Key to Remission

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# Aims

- Understand how to diagnose early RA in patients presenting with arthritis of recent onset
- Appreciate the change in paradigm in managing RA
- Aware of the possibility of remission in patients with early RA

# Outline

- How do we make a diagnosis of early RA?
- Change of treatment paradigm
- What is remission in RA?
- How do we achieve remission in early RA?
- Experience from CUHK Early RA clinic
- Summary

# Case Presentation- polyarthrititis

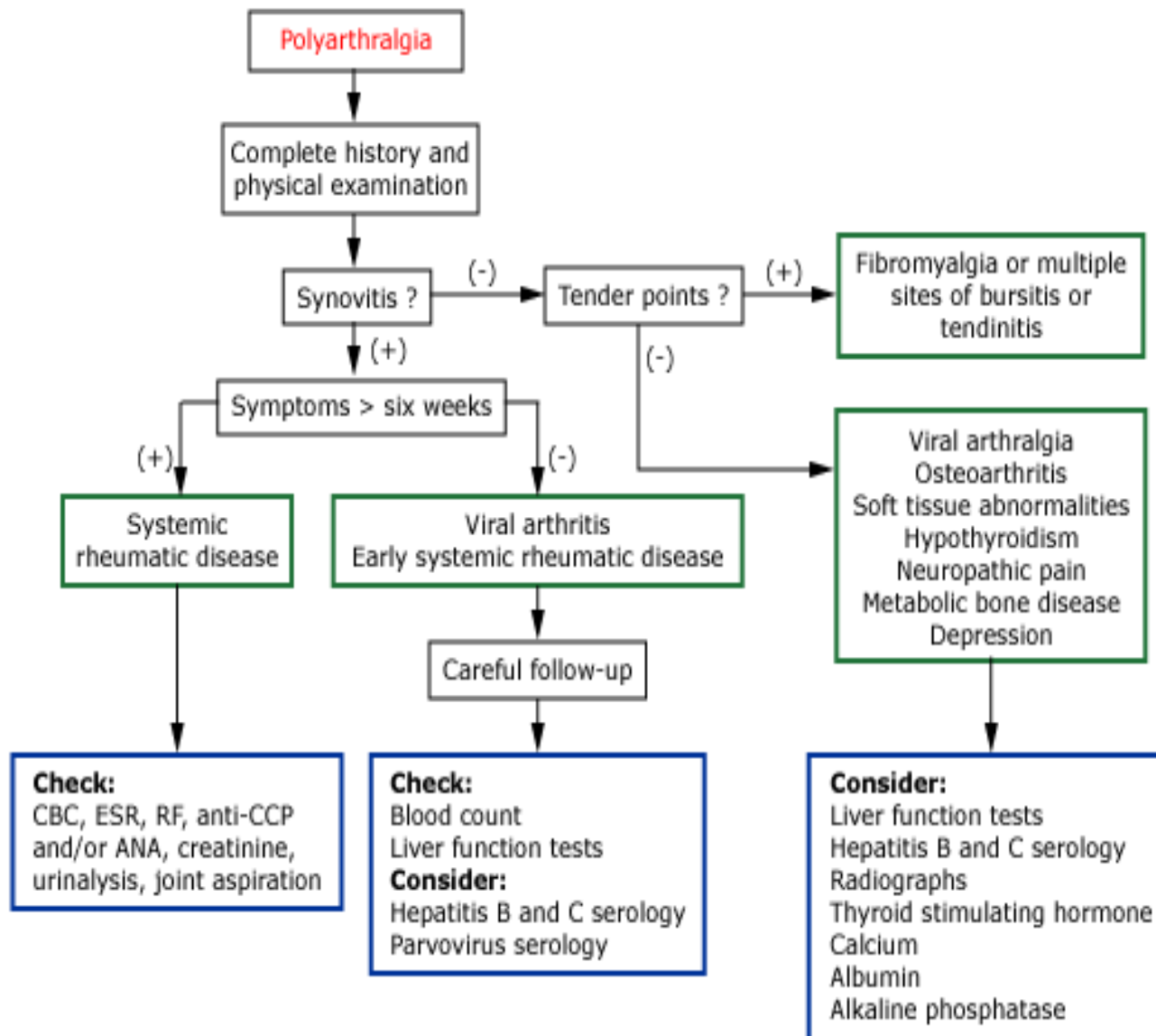
# Case 1

- F/50, housewife
- Right knee arthritis since Feb 2011
- Left knee and bilateral wrist pain Apr 2011
- Morning stiffness > 1 hr
- P/E: afebrile, synovitis over bilateral knee, tenderness of bil. wrists

## Major causes of inflammatory polyarticular rheumatism

<b>Infectious arthritis</b>	<b>Crystal-induced arthritis</b>
Bacterial	<b>Systemic rheumatic illnesses</b>
Lyme disease	Systemic lupus erythematosus
Bacterial endocarditis	Systemic vasculitis
Viral	Systemic sclerosis
Other infections	Polymyositis/dermatomyositis
<b>Postinfectious (reactive) arthritis</b>	Still's disease
Rheumatic fever	Behcet syndrome
Reactive arthritis	Relapsing polychondritis
Enteric infection	Autoinflammatory disorders
<b>Other seronegative spondyloarthritides</b>	<b>Other systemic illnesses</b>
Ankylosing spondylitis	Sarcoidosis
Psoriatic arthritis	Palindromic rheumatism
Inflammatory bowel disease	Familial Mediterranean fever
<b>Rheumatoid arthritis</b>	Malignancy
<b>Inflammatory osteoarthritis</b>	Hyperlipoproteinemias

## Evaluation of polyarthritis or polyarthralgia



# Case 1

- Right knee tap → negative for crystal, WCC > 10,000 /ml
- ↑↑ESR > 100 mm/ hr, CRP 115 mg/L
- RF -ve
- X-ray – no erosion seen
- ??RA



**TABLE 1: 1987 ACR Classification Criteria For RA**

1987 Classification Criteria	
Criteria	<ol style="list-style-type: none"><li>1. Morning stiffness (at least one hour)</li><li>2. Arthritis in three or more joint areas</li><li>3. Arthritis of hand joints (<math>\geq 1</math> swollen joints)</li><li>4. Symmetric arthritis</li><li>5. Rheumatoid nodules</li><li>6. Serum RF</li><li>7. Radiographic changes (erosions) on X-rays of hands</li></ol>
Applicable for	All arthritis patients
Results in	Classification of RA (yes/no)
Positive in case	Four of the seven criteria must be present. Criteria one through four must have been present for at least six weeks.
Test characteristics	Sensitivity of 79%–80% and specificity of 90%–93% for established RA. Sensitivity of 77%–80% and specificity of 33%–77% for early RA.

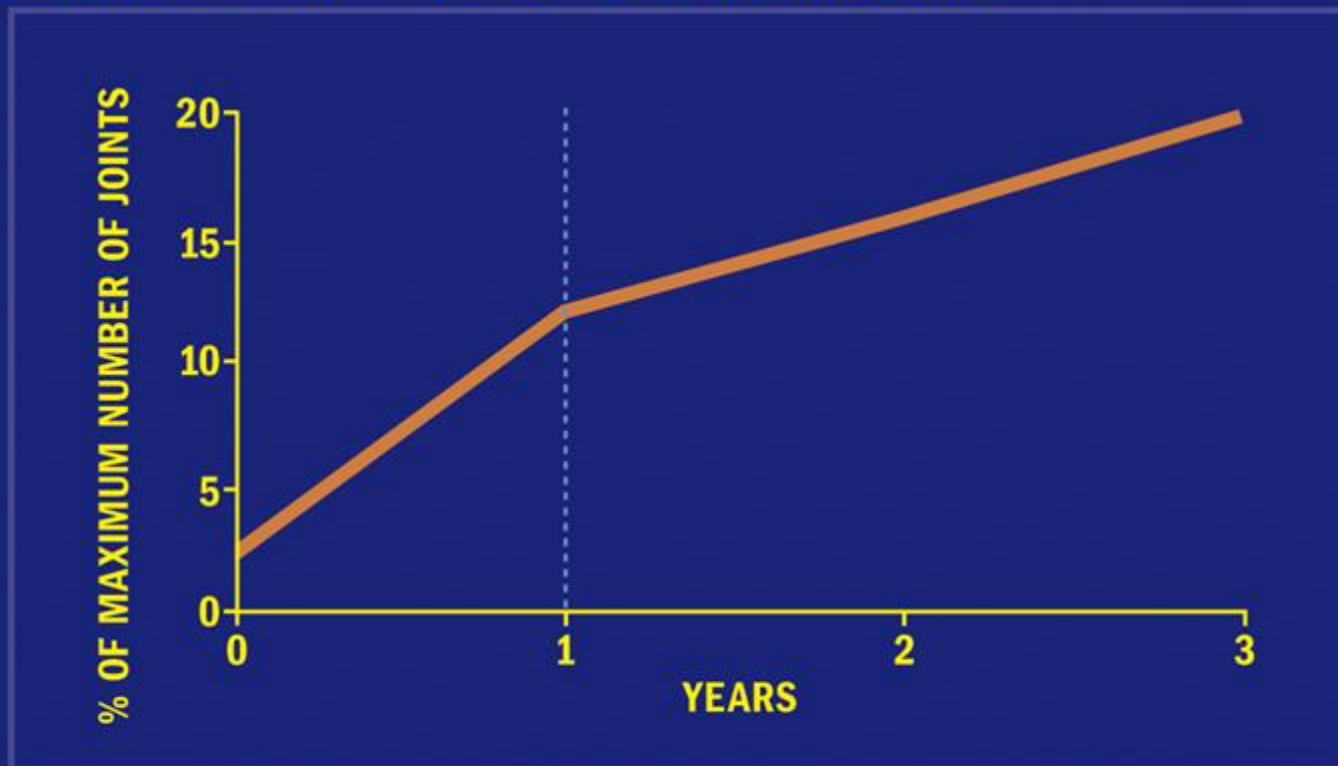




Is the patient having RA?

# Early occurrence of joint damage

Radiographic Progression of Disease During First 3 Years<sup>1</sup>

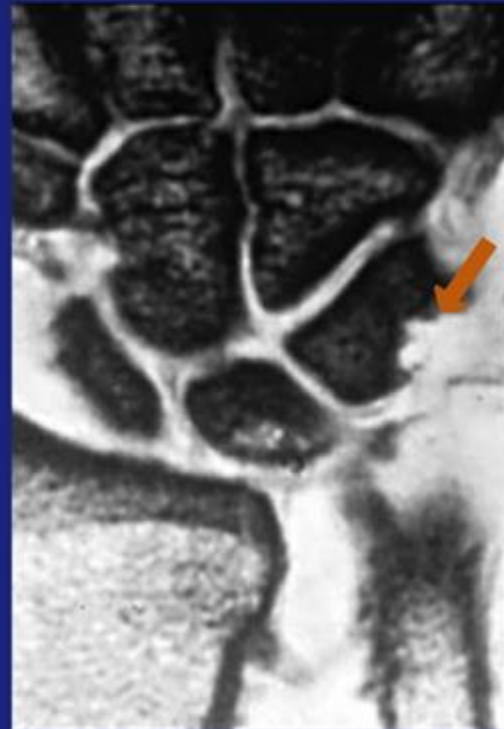


Reference: 1. van der Heijde DMFM, van Leeuwen MA, van Riel PLCM, et al. *J Rheumatol.* 1995;22:1792-1796.

## Early detection of joint damage



Erosion not detectable on x-ray of the wrist in a patient with early active RA<sup>1</sup>

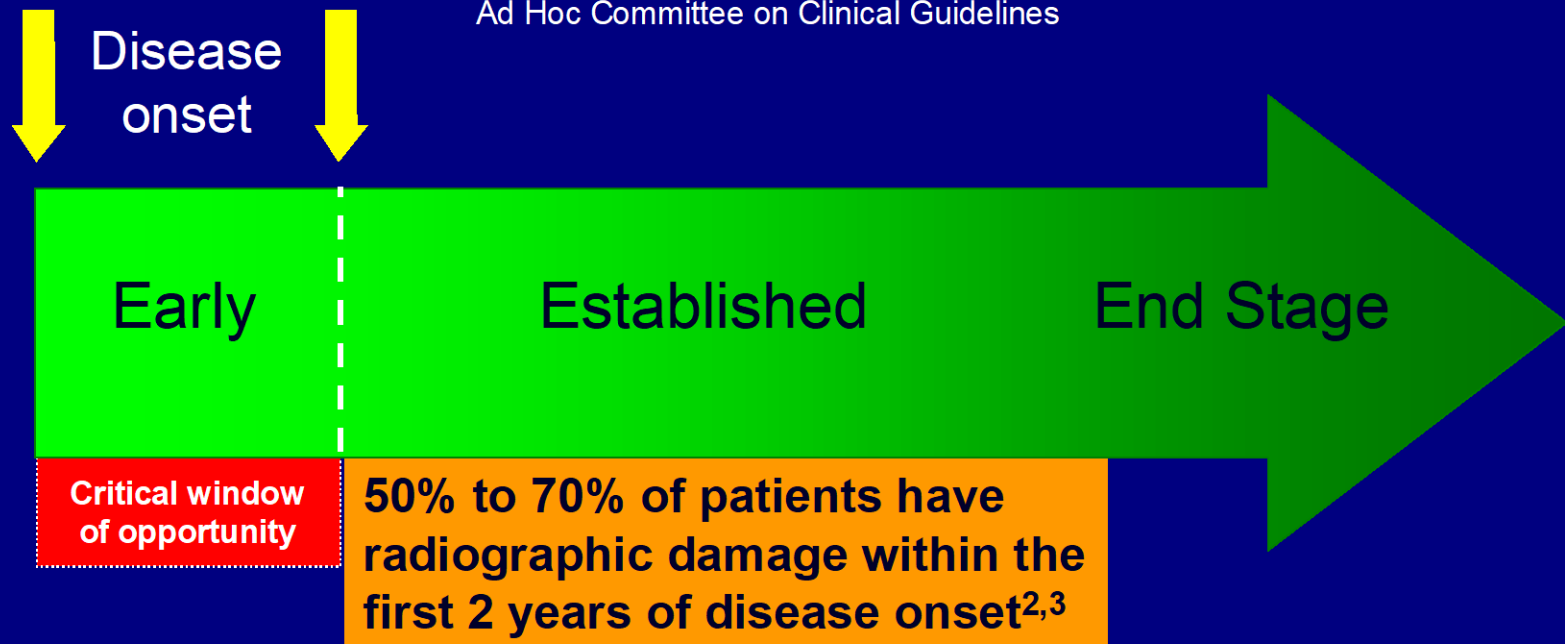


Detectable erosion on MRI of the wrist in the same patient<sup>1</sup>

# ACR Recommendations: Early Aggressive Treatment of RA

“Successful treatment to limit joint damage and functional loss requires early diagnosis and timely initiation of disease modifying agents. The goal of treatment is to arrest the disease and achieve remission.”<sup>1</sup>

American College of Rheumatology  
Ad Hoc Committee on Clinical Guidelines



1. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. *Arthritis Rheum.* 2002;46:328-346.
2. van der Heijde DM. et al. *Br J Rheumatol.* 1995;34(suppl 2):74-78.
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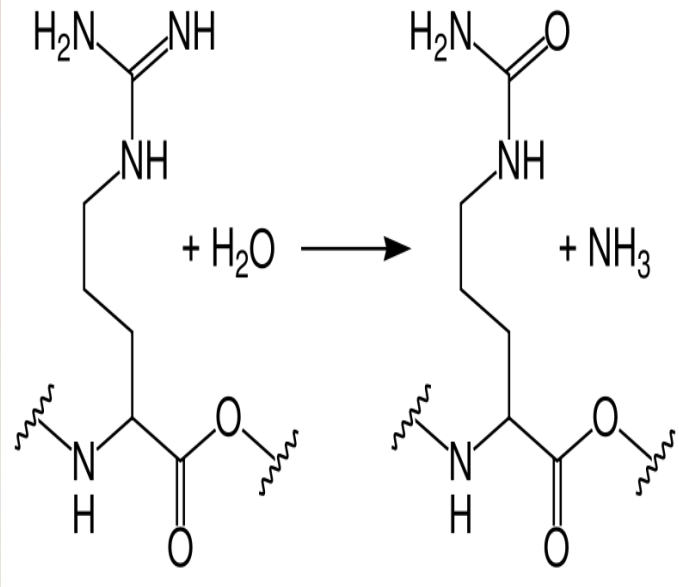
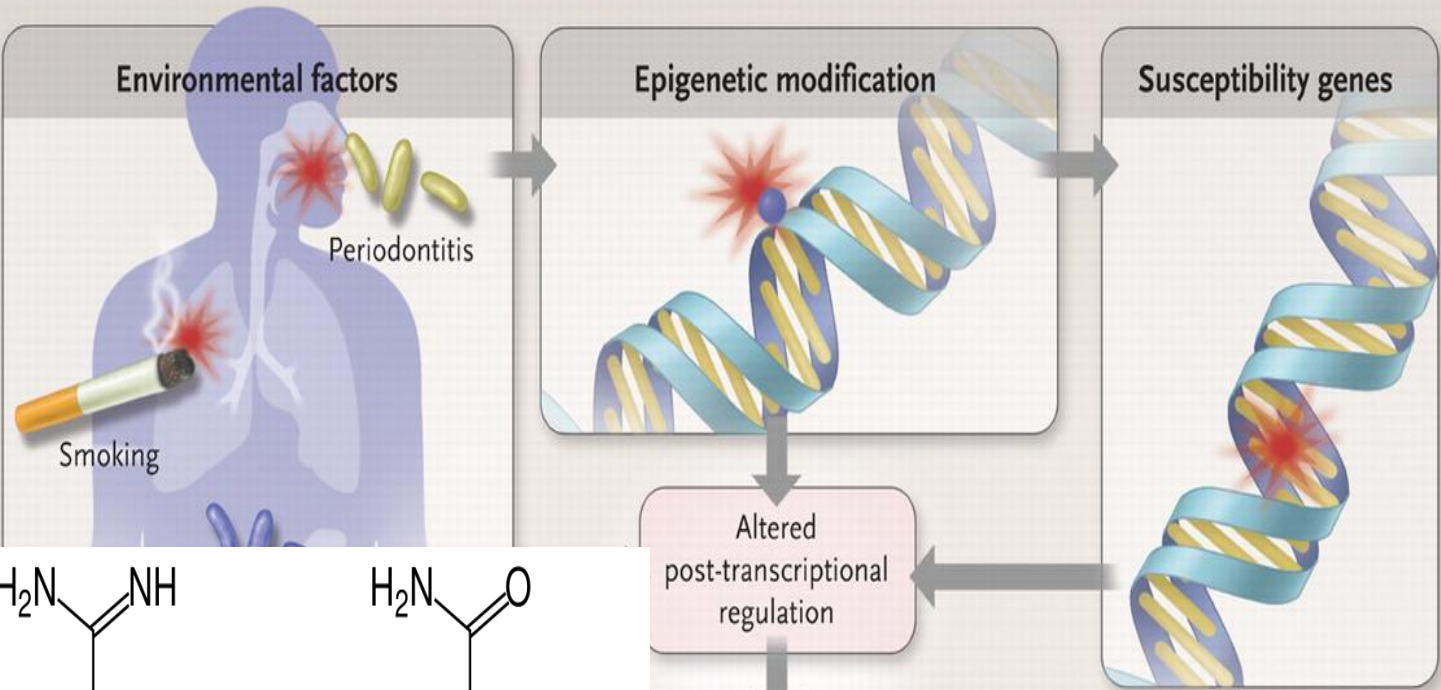
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# How do we diagnose and treat inflammation early?

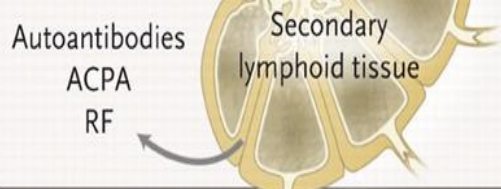
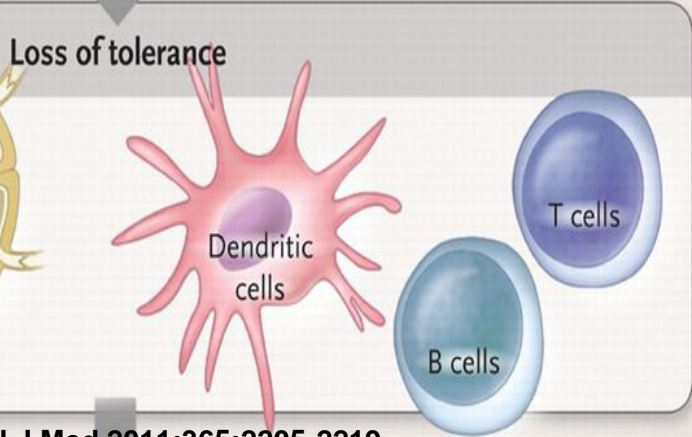


Preadthritis phase



Altered post-transcriptional regulation

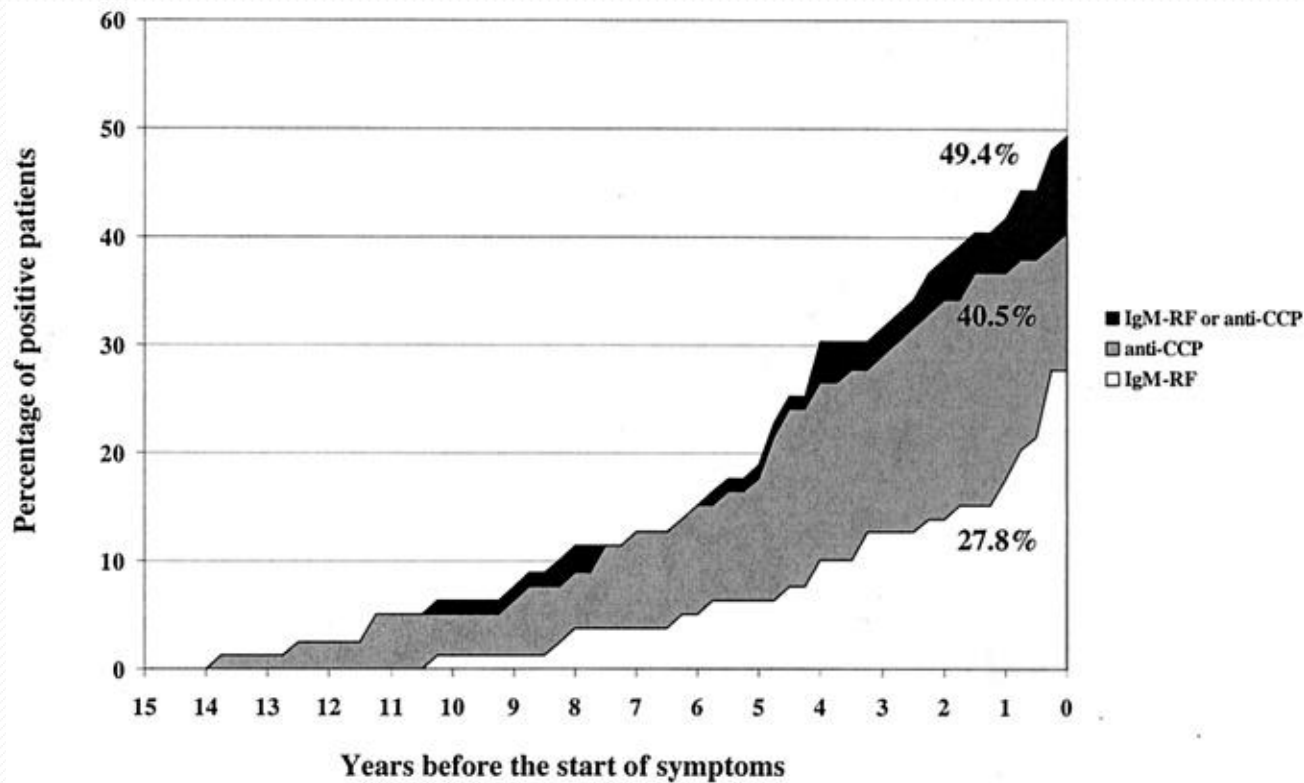
Self-protein citrullination



Time



**Figure 1.** Cumulative percentages of patients with 1 or more positive test results for IgM rheumatoid factor (IgM-RF), anti-cyclic citrullinated peptide (anti-CCP), and IgM-RF and/or anti-CCP before the onset of symptoms of rheumatoid arthritis.



**Table 2. Diagnostic value of IgM-RF and anti-CCP for RA\***

	<b>Blood donor population 0-5 years before symptom onset</b>				<b>Risk of developing RA within 5 years (PPV, %)</b>	
	<b>Sensitivity, %</b>	<b>Specificity, %</b>	<b>PPV, %</b>	<b>NPV, %</b>	<b>General population</b>	<b>† High-risk population</b>
IgM-RF	20.5	98.6	88.2	71.1	1.5	37.7
Anti-CCP	28.9	99.5	96.6	73.5	5.3	69.4
IgM-RF or anti-CCP	36.5	98.1	90.6	75.4	1.9	43.8
IgM-RF and anti-CCP	13.0	100	100	75.4	100	100

\* IgM-RF = IgM rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide; PPV = positive predictive value; NPV = negative predictive value.

† Defined as individuals who have 2 first-degree relatives with rheumatoid arthritis (RA) (5-year incidence of RA among such individuals has been reported to be 3.9%)

# New autoantibody: Anti-cyclic citrullinated peptide (anti-CCP)

- Citrulline - a post-translationally modified arginine residue
- Ab against keratin or filaggrin
- Sensitivity and specificity of CCP vs RF: 67 vs 69 and 95 vs 85 percent for RA, respectively

<b>Negative</b>	<b>Low/weak positive</b>	<b>Moderate positive</b>	<b>High/strong positive</b>	<b>Unit</b>
< 20 <sup>[20]</sup>	20 - 39 <sup>[20]</sup>	40 - 59 <sup>[20]</sup>	> 60 <sup>[20]</sup>	EU <sup>[20]</sup>

# Utility for diagnosing early RA

- In early RA, the prevalence of RF is 50–66%, and anti-CCP is 41–48%; (normal population: 7–13% and 3–9% respectively)
- Predict damage as indicated by MRI
- Associated with radiographic progression of disease

## 2010 ACR/EULAR classification criteria

### New classification criteria

Scoring  $\geq 6$  points.

In the presence of erosiveness  
seen in light of an inflammatory  
disorder, no other points need  
to be obtained for the  
classification of RA

1. Joint involvement (0–5)
  - 1 medium–large joint (0)
  - 2–10 medium–large joints (1)
  - 1–3 small joints (large joints not counted) (2)
  - 4–10 small joints (large joints not counted) (3)
  - >10 joints (at least one small joint) (5)
2. Serology (0–3)
  - Negative RF and negative ACPA (0)
  - Low positive RF or low positive ACPA (2)
  - High positive RF or high positive ACPA (3)
3. \*Acute phase reactants (0–1)
  - Normal CRP and normal erythrocyte sedimentation rate (ESR) (0)
  - Abnormal CRP or abnormal ESR (1)
4. Duration of symptoms (0–1)
  - <6 weeks (0)
  - $\geq 6$  weeks (1)

# 2010 ACR/EULAR Classification Criteria for RA

- DIP, 1st MCP, 1st MTP are excluded from assessment
- Large joints: shoulders, elbows, hips, knees and ankles
- Small joints: MCPs, PIPs, MTPs, 1st IPs, wrists ( with the above exceptions)

# Case 1

- With the 2010 ACR/ EULAR classification criteria:
  - 2 small and 2 large joints
  - Anti-CCP: 200 EU (high +ve)
  - elevated acute phase reactants
  - Duration > 6 weeks
  - RA?

# Case 1

- With the 2010 ACR/ EULAR classification criteria:
  - 2 small and 2 large joints → 2
  - Anti-CCP: 200 EU (high +ve) → 3
  - elevated acute phase reactants → 1
  - Duration > 6 weeks → 1
  - total scores: 7/10
  - RA





# Any other investigations? Imaging

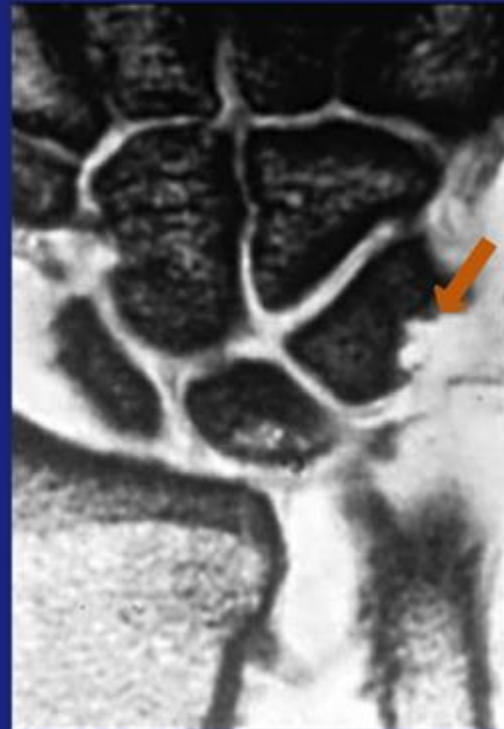
USG

MRI

## Early detection of joint damage

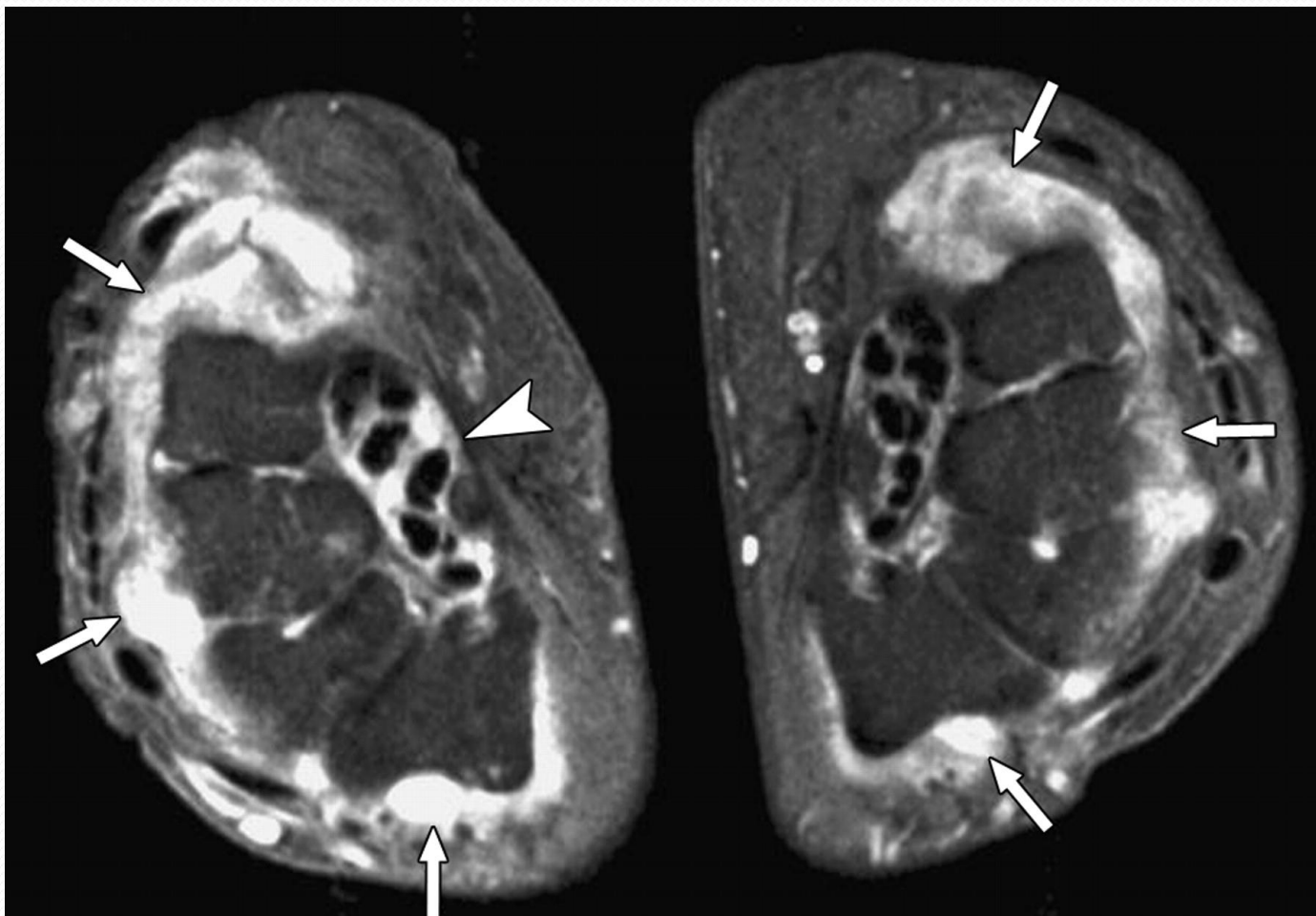


Erosion not detectable on x-ray of the wrist in a patient with early active RA<sup>1</sup>



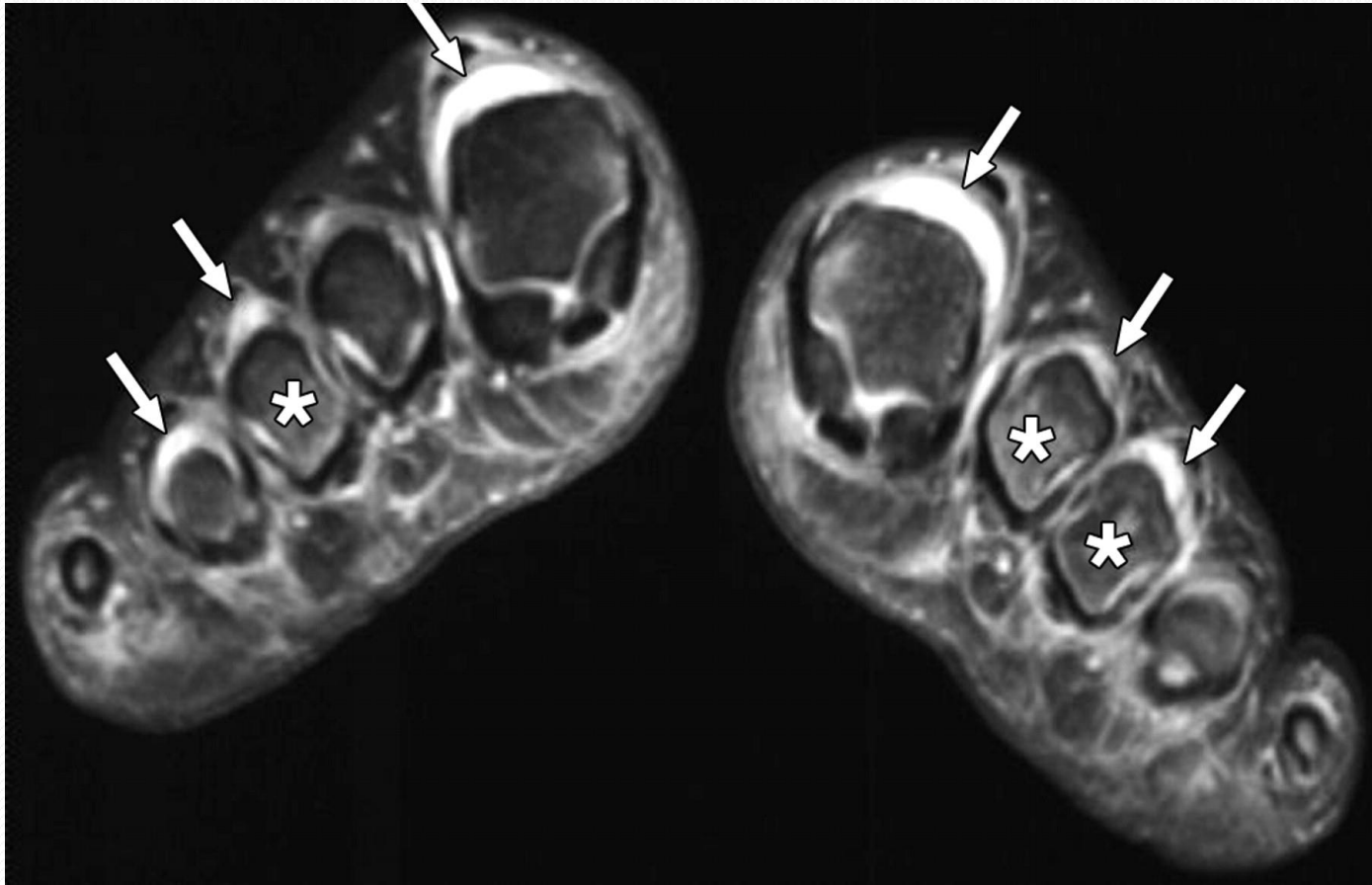
Detectable erosion on MRI of the wrist in the same patient<sup>1</sup>

34-year-old woman with early rheumatoid arthritis and synovitis



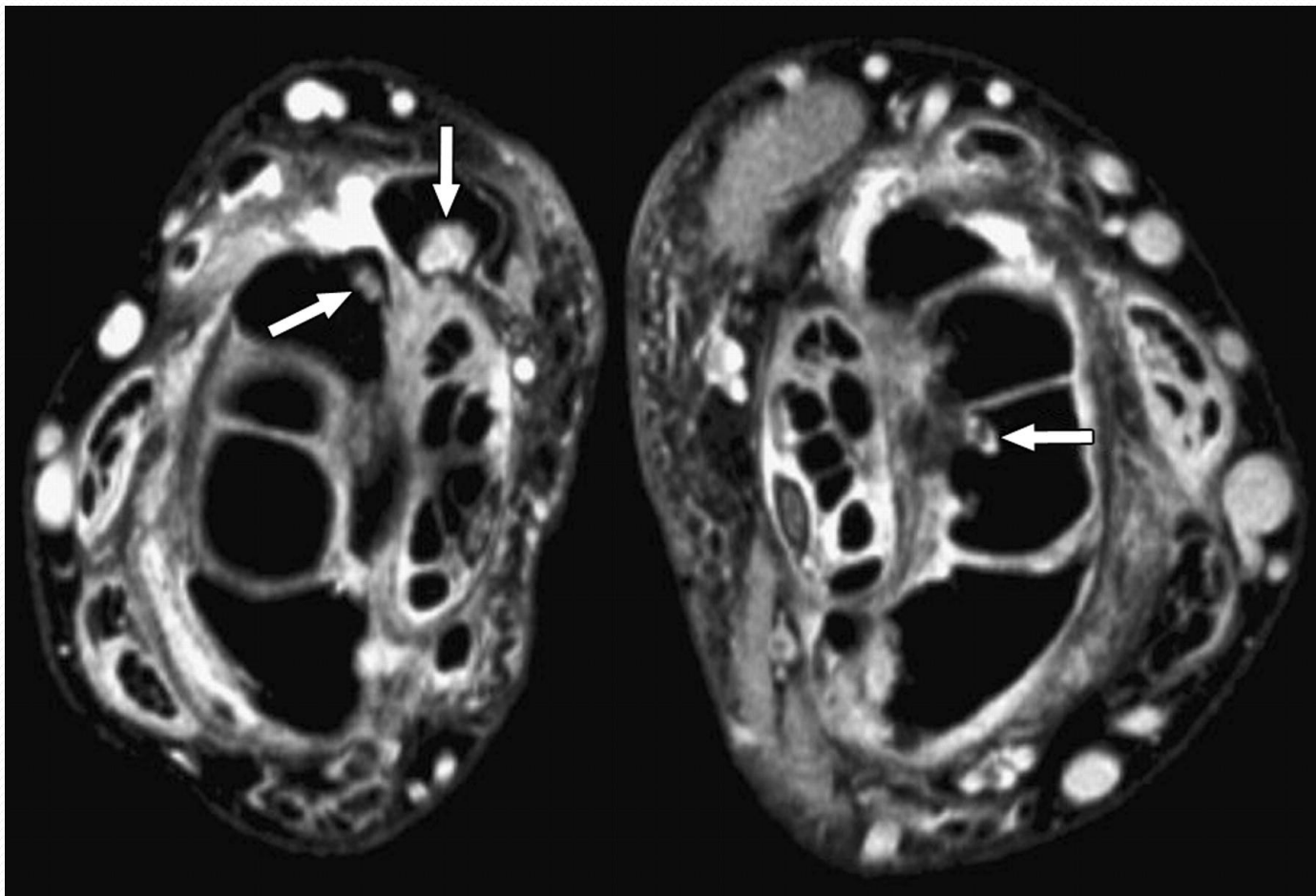
Boutry, N. et al. Am. J. Roentgenol. 2007;189:1502-1509

## 34-year-old woman with early rheumatoid arthritis and synovitis



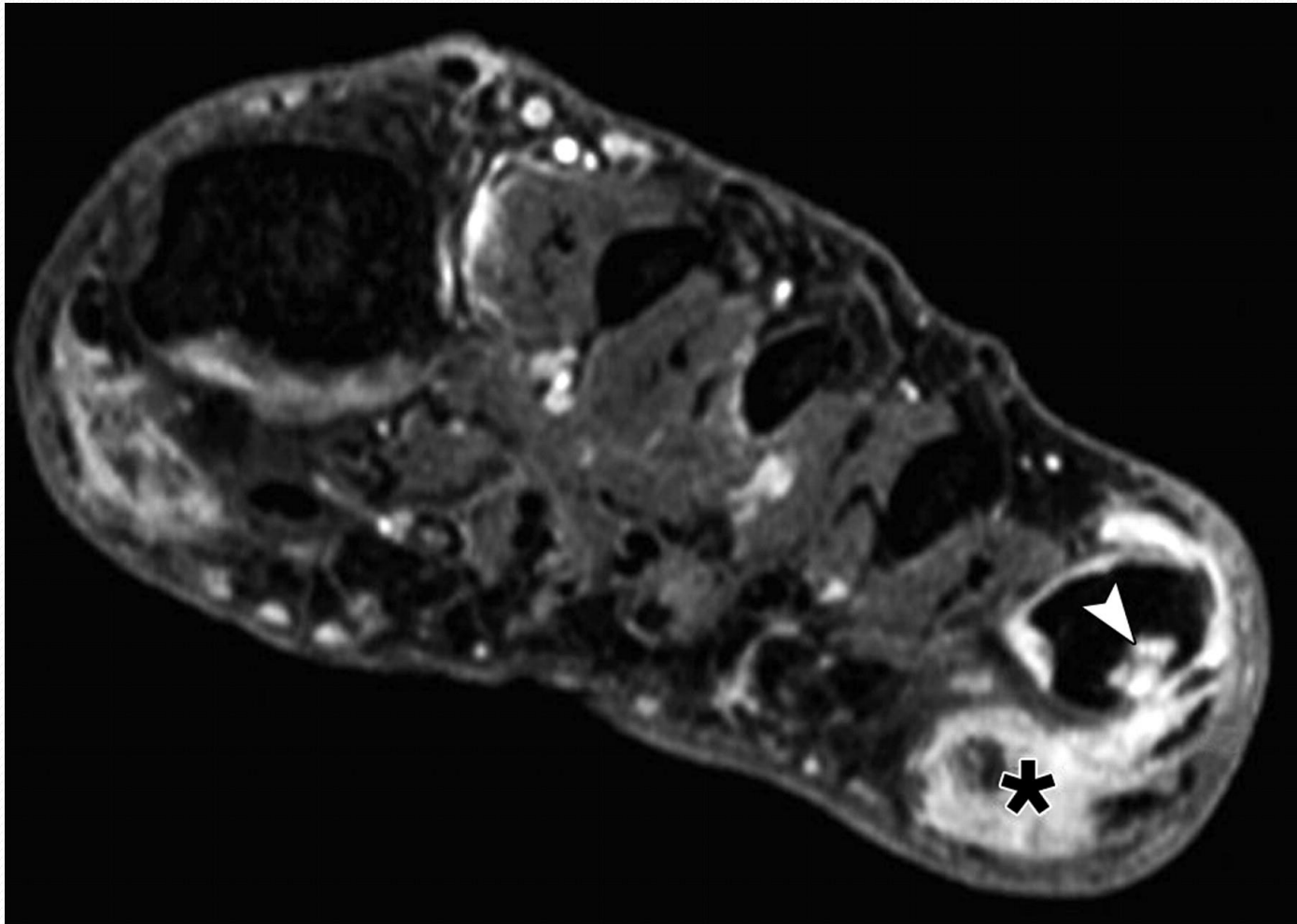
Boutry, N. et al. Am. J. Roentgenol. 2007;189:1502-1509

**38-year-old woman with early rheumatoid arthritis and bone erosions**



**Boutry, N. et al. Am. J. Roentgenol. 2007;189:1502-1509**

**38-year-old woman with early rheumatoid arthritis and bone erosions**



**Boutry, N. et al. Am. J. Roentgenol. 2007;189:1502-1509**

**33-year-old man with early rheumatoid arthritis and bone marrow edema**




Boutry, N. et al. Am. J. Roentgenol. 2007;189:1502-1509

# MRI in early RA

- More sensitive in picking up erosion
- Patients with -ve RF/CCP
- Expensive
- Indication to allow initiation of aggressive therapy



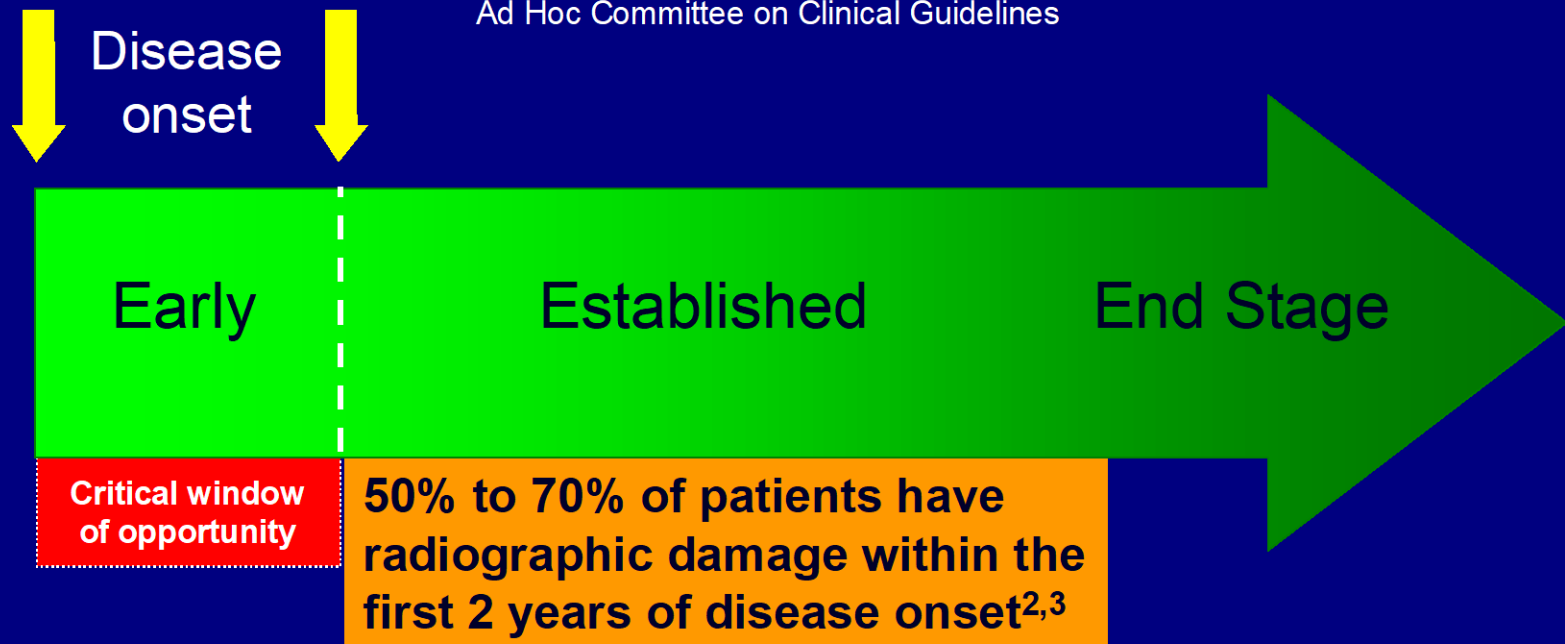


Early rheumatoid arthritis-is  
there a window of  
opportunity?

# ACR Recommendations: Early Aggressive Treatment of RA

“Successful treatment to limit joint damage and functional loss requires early diagnosis and timely initiation of disease modifying agents. The goal of treatment is to arrest the disease and achieve remission.”<sup>1</sup>

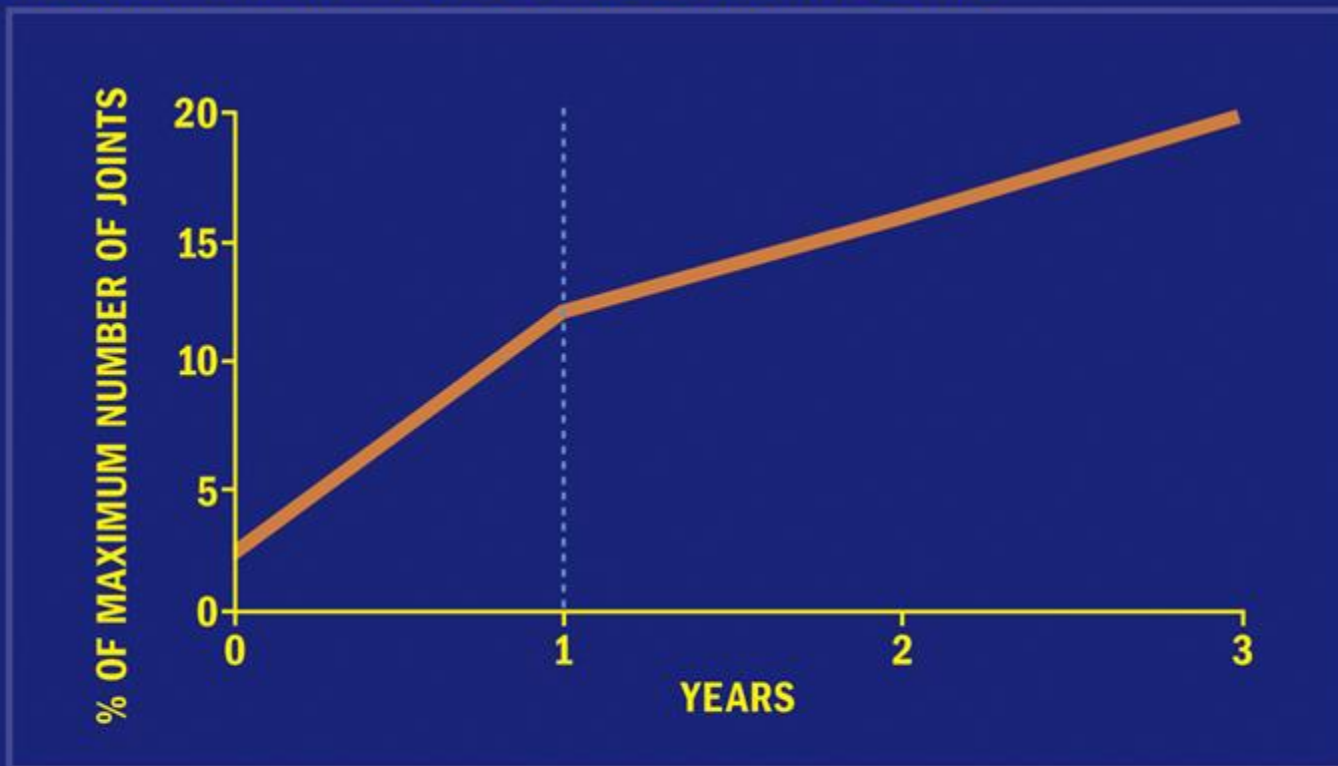
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# Early occurrence of joint damage

Radiographic Progression of Disease During First 3 Years<sup>1</sup>

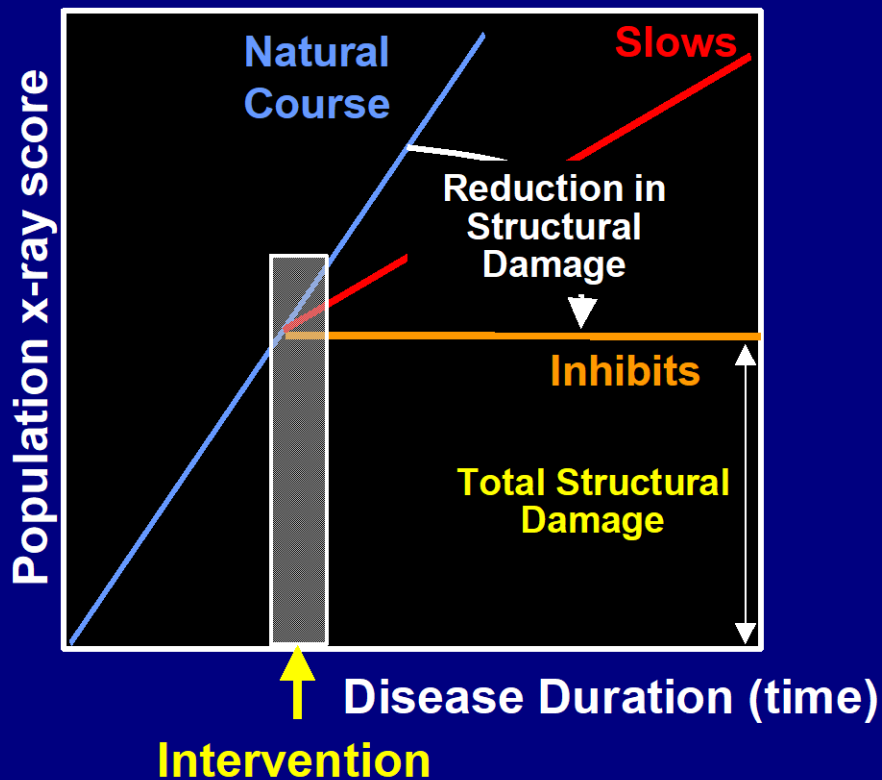


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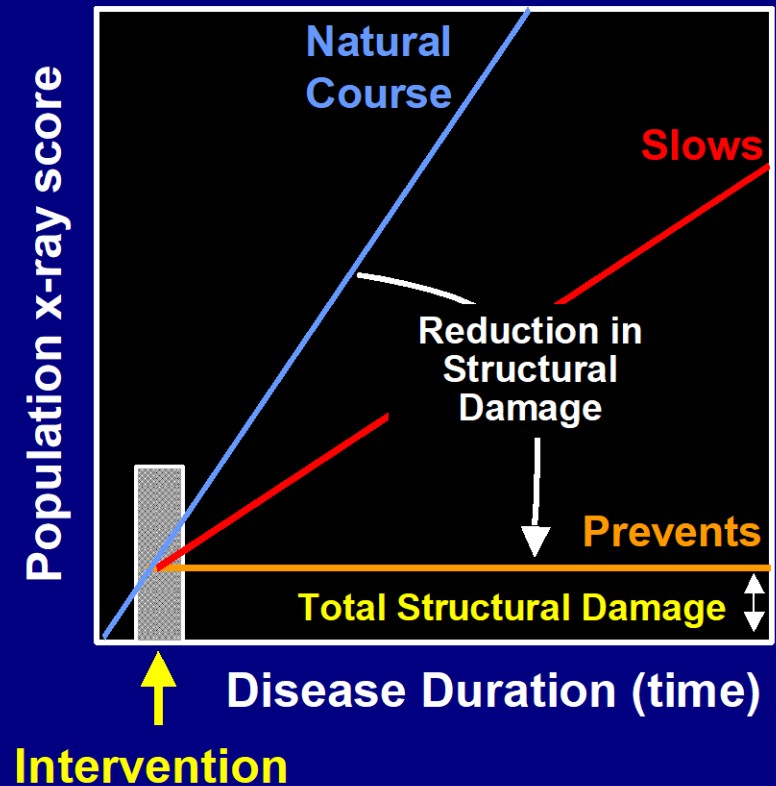
# Altering the Natural Course of RA

## Potential for Early Aggressive Therapy

### Established Disease Model



### Early Aggressive Therapy



# Definitions of Early Rheumatoid Arthritis

- Definition is evolving
- Based on clinical studies, definitions range from disease duration of <3 months to < 5 years from onset of symptoms
- Within the first 2 years of disease onset, 50% to 70% of patients have radiographic damage<sup>1,2</sup>

# The evolving RA treatment paradigm

## CURRENT APPROACH

### INITIAL TREATMENT

Traditional  
DMARDs



### IF POOR RESPONSE

Add additional  
DMARDs

Add biologic  
agent

## EVOLVING PARADIGM

### INITIAL TREATMENT

Aggressive  
DMARD  
dosage

Biologic  
agent

Monotherapy or Combination



### IF POOR RESPONSE

Combination  
therapy



### IF DISEASE CONTROLLED

Discontinuation/  
reduction of  
DMARDs

# Patient # 2

- 50 yr old female
- Pain and swelling in the hands, elbows, knees with EMS 2 hr x 3 months
- Some improvement with NSAID
- P/E: 6 tender joints, 4 swollen joints
- Ix:CRP:17.9, ESR 38, RF:160
- X-rays: no erosion
- How do we assess her disease activity?





# What is our goal? Remission !

- Clinical Remission
  - Normal acute phase response
  - No clinical synovitis
  - DAS 28 <2.6
- Imaging Remission
  - No significant synovitis on sensitive imaging
- True Remission
  - A state of no detectable disease with no progression of structural damage

# How would you treat?

1. MTX then Lef/SLZ/CSA (sequential)
2. MTX then MTX+ SSZ + HCQ (step up)
3. MTX+ SLZ + pred
4. MTX+ TNF blocker

# New Treatment Paradigm

- Aggressive Treatment
- Tight control

# Aggressive Treatment

- Early rheumatoid arthritis
  - Disease activity is less severe
  - A smaller load of inflammatory cells
  - More responsive to treatment
- Aggressive treatment during this phase is more likely to succeed than in later phase

# Aggressive Treatment

- Treatment of disease in the first month is important to retard radiographic progression

Raza K et al. Best Pract Res Clin Rheumatol 2006;20:849-63

- RA patients with shorter disease duration respond better to treatment

Anderson JJ et al. Arthritis Rheum 2000;43:22-9.

- Important to treat and control the disease as soon as possible after diagnosis

# What is tight control?

- A treatment strategy tailored to the individual patient with RA, which aims to achieve a predefined level of low disease activity or remission within a certain period of time

# What is the advantage of tight control?

- It results in greater improvement and a higher percentage of patients meeting the present aim of low disease activity or remission

Makinen H et al. J Rheumatol 2007;34:316-21

Grigor C et al. Lancet 2004;364:263-9

Goekoop-Ruiterman YP et al. Ann Intern Med 2007;146:406-15

# Behandel Strategieën (BeSt) Study

- 508 patients with active RA of disease onset <2 years
- Patients were randomized in 4 strategies
  - Sequential DMARD monotherapy
  - Step-up combination therapy
  - Initial combination therapy with tapered high-dose prednisolone
  - Initial combination therapy with TNF antagonist infliximab



time (months)	Group 1 sequential monotherapy n=126	Group 2 step-up combination n=121	Group 3 initial combination n=133	Group 4 initial infliximab+MTX n=128
0	MTX 15 mg/wk	MTX 15 mg/wk	MTX 7.5 mg/wk + SSA + pred 60 to 7.5 mg/day	MTX 25 mg/wk + infliximab 3 mg/kg/8wk
3	↓ MTX 25 mg/wk	↓ MTX 25 mg/wk	↓ MTX 25 mg/wk + SSA + pred 7.5	↓ MTX+infix 6 mg/kg
5	↓ SSA 1000 mg bid	↓ MTX + SSA 1000	↓ MTX+ CsA + pred	↓ MTX+ infix 7.5 mg/kg
6	↓ leflunomide 20 mg/day	↓ MTX+SSA+HCQ 400 mg/day	↓ MTX + infliximab 3 mg/kg	↓ MTX+infix 10 mg/kg
7	↓ MTX 25 mg/wk + infliximab 3 mg/kg	↓ MTX+SSA+HCQ + pred 7.5 mg/day	↓ MTX + infliximab 6 mg/kg	↓ SSA 1000 mg bid
9	↓	↓	↓	↓ leflunomide 20 mg/day
12	↓	↓	↓	↓
up to 5 yrs	↓ ↓	↓ ↓	↓ ↓	↓ ↓

# BeSt Treatment Strategies

## Basics

- Compare 4 strategies, not therapies
- Change therapy if not effective, aiming at DAS  $\leq 2.4$
- Taper to minimum therapy after success
- Restart last effective strategy if success is lost

Changes in medication over time in **A.** sequential monotherapy, **B.** step up to combination therapy, **C.** initial combination therapy including prednisone, **D.** initial combination therapy including infliximab.

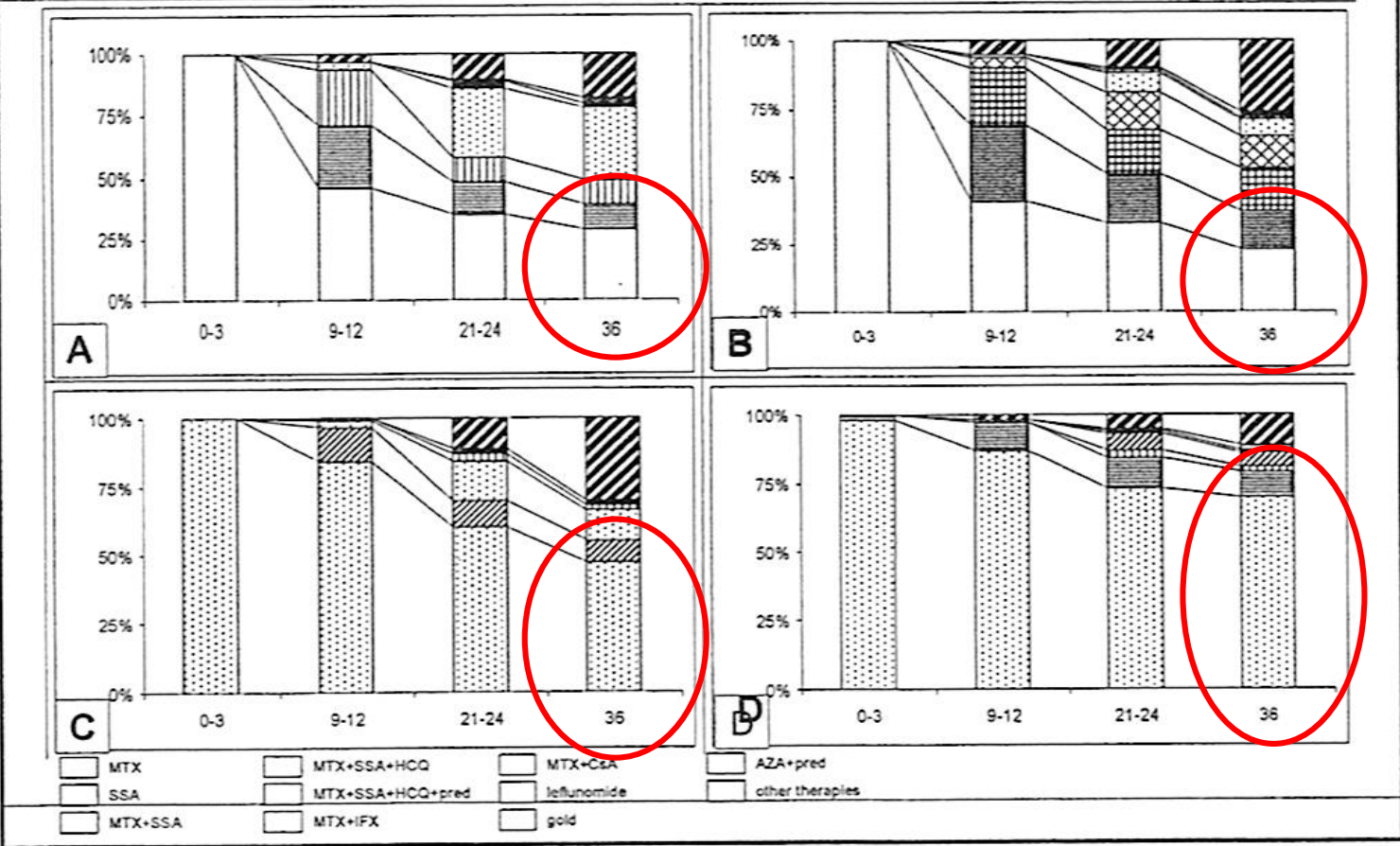
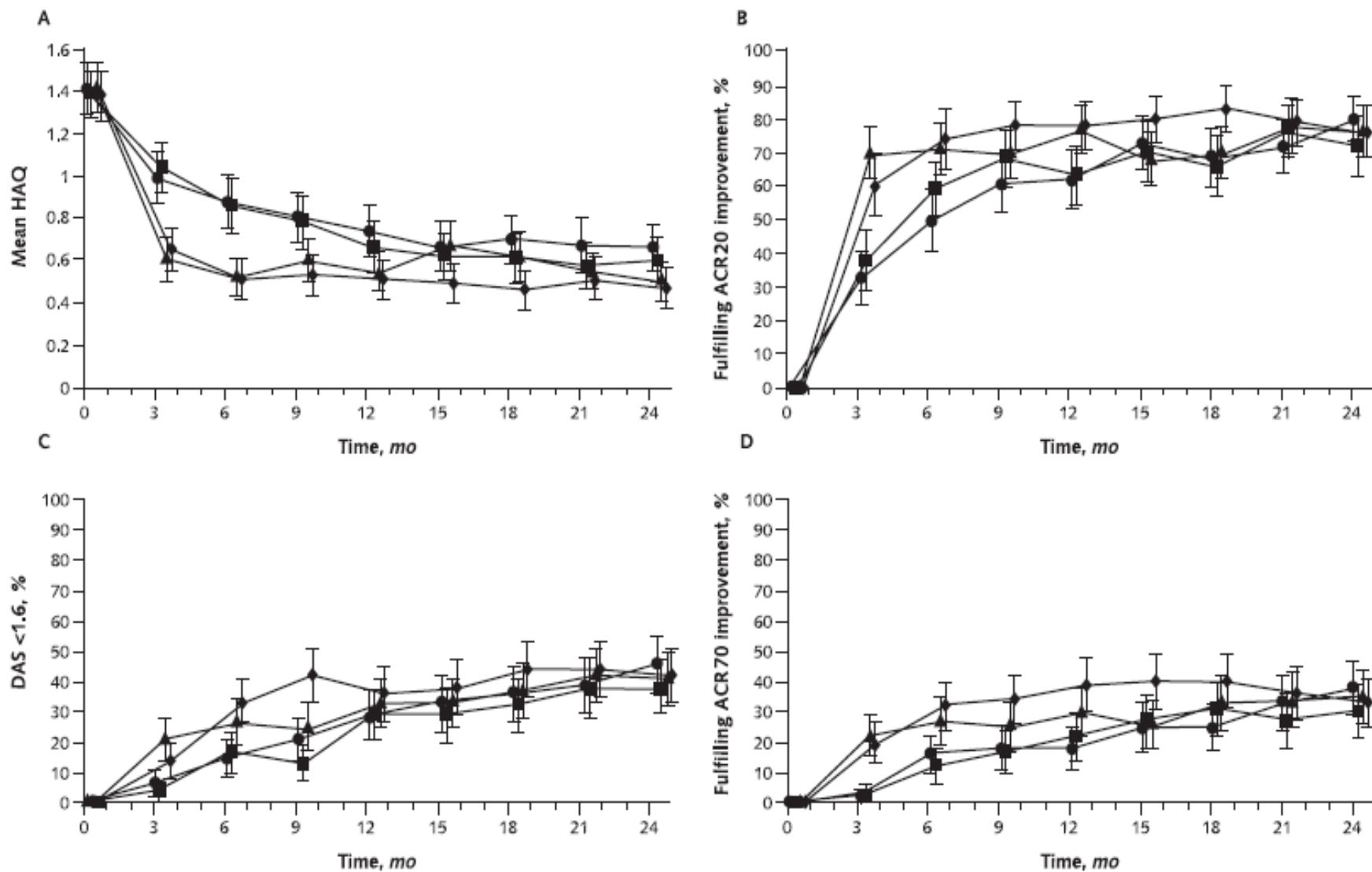


Figure 3. Clinical and radiographic efficacy outcomes during 2 years of follow-up.



- Radiological damage progression
  - Remained low in all groups
  - Significantly lower in initial combination-therapy groups than in initial monotherapy groups

# Patient Preference

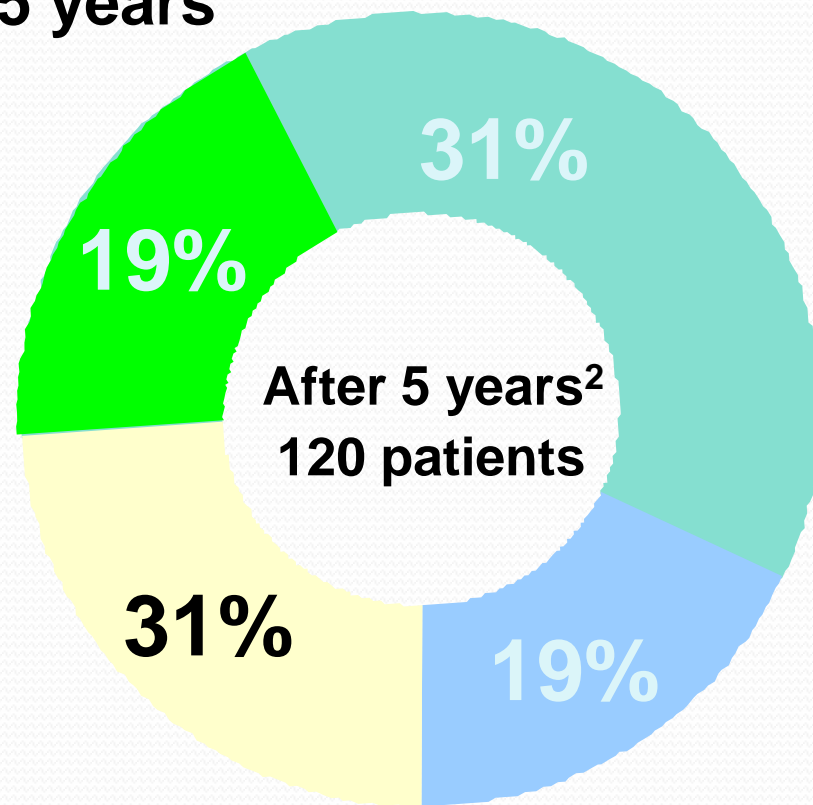
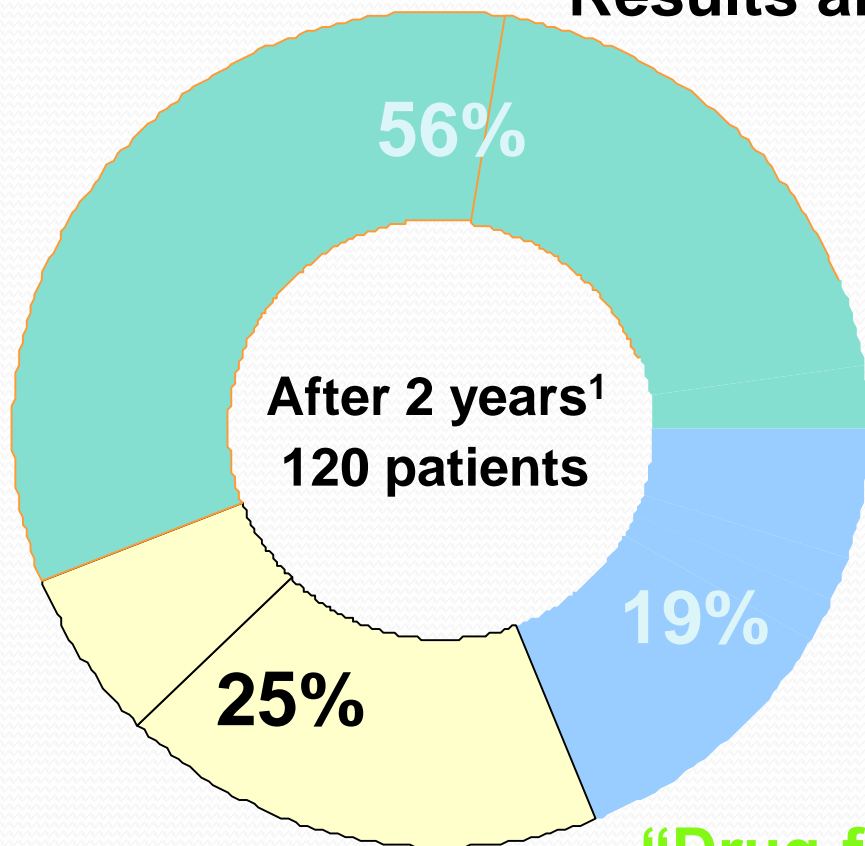
- Most patients didn't like combination therapy with prednisolone because of the side effects

- Clinical remission ( $DAS < 1.6$ ) in 4 treatment strategies
  - 29-36% after first year
  - 38-46% after second year
- Low disease activity ( $DAS \leq 2.4$ )
  - 79% after two year

# BeSt Strategy Group 4

## Achieving Long-term Remission

### Results after 5 years



Responders (off IFX)

Responders (continued IFX)

Non-responders/AE

<sup>1</sup>van der Bijl et al., Arthritis Rheum 2007;56(7):2129-2134;

<sup>2</sup>Klarenbeek et al. EULAR 08 Data from the poster abstract THU0162



# Our aim is to achieve remission

	Intensive Tx	Conventional Tx
CAMERA	50%	37%
TICORA	65%	16%
FIN-RACo	51%	16%
BeSt	38-46%	13-36%
COMET	50%	28%
MTX+ABA	41.4%	23.3%



# How do I treat my patients? Hong Kong Experience

CUHK ERA clinic

# Infliximab is Associated with Improvement in Arterial Stiffness in Patients with Early Rheumatoid Arthritis — A Randomized Trial

LAI-SHAN TAM, QING SHANG, EDMUND K. LI, SHANG WANG, RUI-JIE LI, KA-LAI LEE, YING-YING LEUNG, KING-YEE YING, CHEUK-WAN YIM, EMILY W. KUN, MOON-HO LEUNG, MARTIN LI, TENA K. LI, TRACY Y. ZHU, RICKY K. CHUI, LORRAINE TSEUNG, SHUI-LIAN YU, WOON-PANG KUAN, and CHEUK-MAN YU

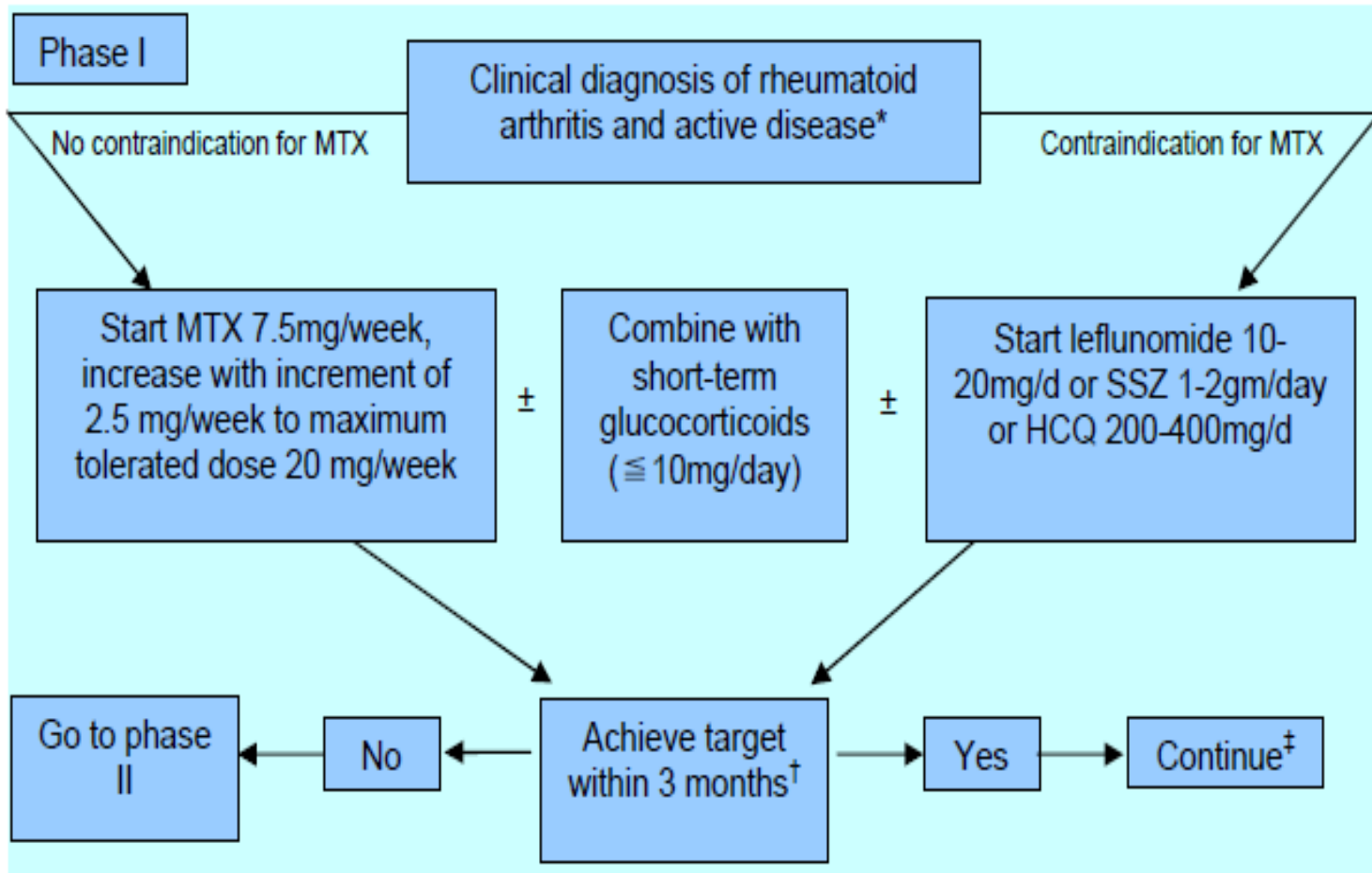
DAS remission at 6 months:

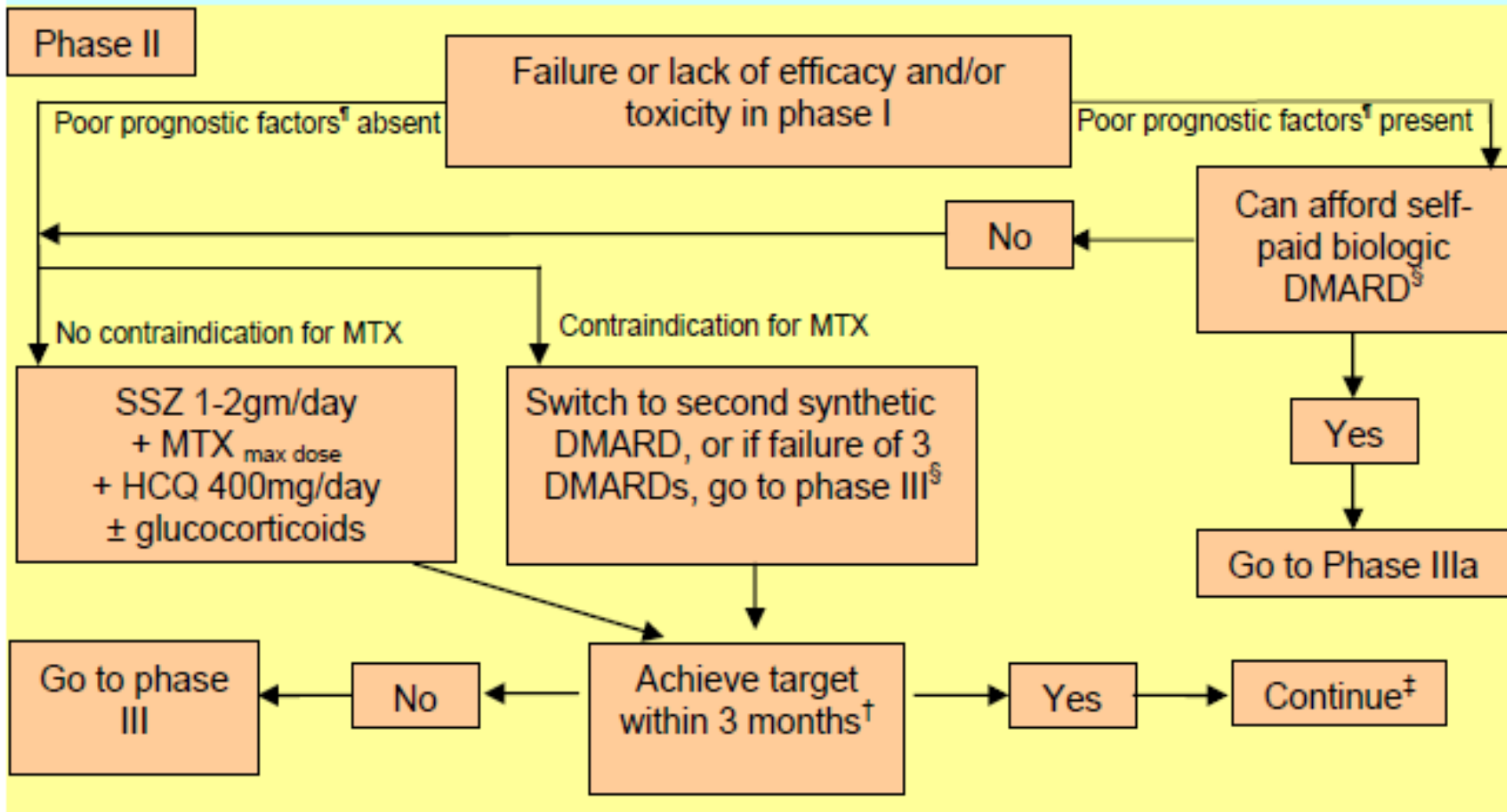
- 5/20 (25%) MTX alone group
- 9/20 (45%) MTX + infliximab group respectively  
( $p > 0.05$ )

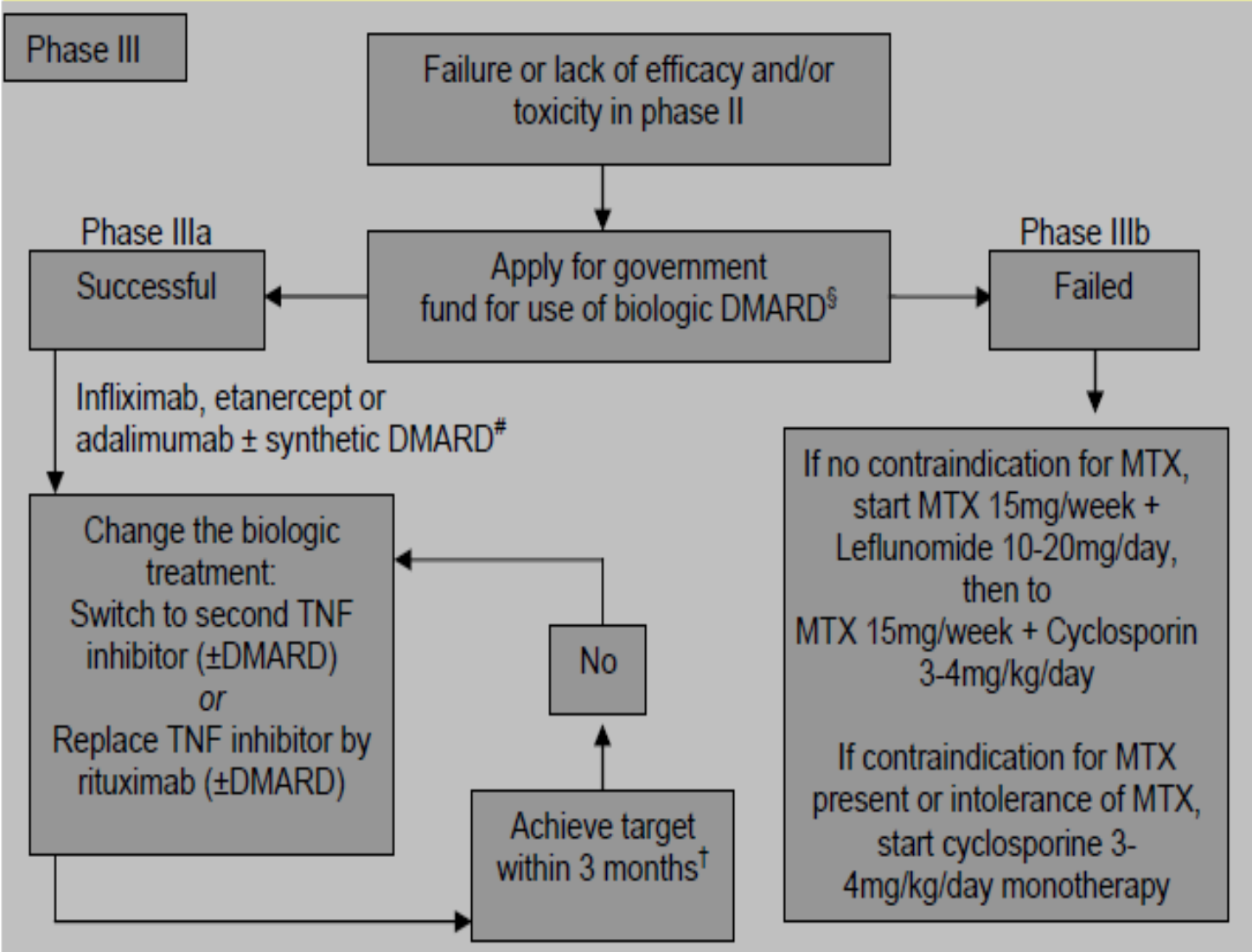
*The Journal of Rheumatology 2012; 39:12; doi:10.3899/jrheum.120541*

# Serum Soluble Receptor for Advanced Glycation End Products Levels and Aortic Augmentation Index in Early Rheumatoid Arthritis—A Prospective Study

Lai-Shan Tam, MD,\* Qing Shang, PhD,\* Edmund K. Li, MD,\*  
Shang Wong, PhD,\* Rui-Jie Li, PhD,\* Ka-Lai Lee, MRCP,<sup>†</sup>  
Ying-Ying Leung, MRCP,<sup>‡</sup> King-Yee Ying, FRCP,<sup>§</sup>  
Cheuk-Wan Yim, MRCP,<sup>||</sup> Emily W. Kun, FRCP,<sup>¶</sup>  
Moon-Ho Leung, FHKCP,\*\* Martin Li, PhD,\* Tena K. Li, BN,\*  
Tracy Y. Zhu, PhD,\* Ricky K. Chui, BEng,\* Lorraine Tseung, BBA,\*  
Shui-Lian Yu, PhD,\* Woon-Pang Kuan, MRCP,\* and  
Cheuk-Man Yu, MD\*







# ACR/EULAR Remission

Boolean definition:

- tender joint count, swollen joint count, CRP (mg/dl) level, and patient global assessment  $\leq 1$

Simplified Disease Activity Score  $\leq 3.3$

- TJC + SJC + patient global assessment + physician global assessment + CRP (mg/dl)



# Results at 12 months:

Out of 94 patients:

- 53 (56.4%) DAS remission
- 18 (19.1%) Boolean-based
- 21 (22.3%) SDAI remission

# Changing Paradigm in RA Treatment

- Goals
  - To achieve remission
- Tools
  - Conventional DMARDs
  - Biologics
- Process
  - Reliable diagnosis
  - Early treatment
  - Aggressive therapy approach
  - Disease activity measurement (eg.DAS)

# Take Home Message

- Remarkable improvement of clinical signs and symptoms in early RA could be achieved by using currently available drugs when treatment adjustments are made systematically and according to disease activity measurements

# Thank you!

