Early Arthritis Workshop

The clock is ticking

Andrew Harrison

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HoD, Wellington Regional Rheumatology Unit

The purpose of this workshop

By the end of this session you should be able to:

- understand the significance of early treatment of RA
- recognise the key diagnostic features of early RA
- recognise the risk factors for poor prognosis
- develop a structured approach to assessment of early arthritis

Case 1

Amanda, 35 years.
presents with 2 week history of pain, EMS, swelling hands and feet

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Undifferentiated polyarthritis

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Is that all we need to know?

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Undifferentiated polyarthritis

Is that all we need to know?

Advantages of classification

- prognosis
- specific management
- urgency of management
- reference point

Case 1

Undifferentiated peripheral inflammatory arthritis

- differential diagnosis
  - rheumatoid arthritis
  - reactive arthritis
  - osteoarthritis
  - psoriatic arthritis
  - viral arthritis
  - crystal arthritis
  - spondyloarthropathy (undiff, AS)
  - connective tissue disease
  - sarcoidosis
  - polymyalgia rheumatica
  - Lyme disease
  - paraneoplastic
  - hepatitis
  - endocrine-related
  - fibromyalgia/pain syndrome
  - systemic autoimmune disease

Bombardier C, van der Heijde DM. How to investigate and follow up undifferentiated peripheral inflammatory arthritis? 3e initiative 2008-2009: systematic reviews and clinical algorithm. *J Rheumatol Suppl* 2011;87:1-2.

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Amanda, 35 years, UPIA

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Why is it important to diagnose and treat RA early?

- Early treatment is dependant on early diagnosis
- If there was no effective Rx, early diagnosis wouldn't matter
- If there were effective Rx but no benefit in early Rx, early diagnosis wouldn't matter

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- What is the evidence that delaying treatment is harmful?

Why is it important to diagnose and treat RA early?

Trials of treatment strategies

- Egmose 1995. Early RA - immediate HCQ v 8 month delay
- at 5 years, differences in outcome measures were sustained
- demonstrated a “therapeutic window”

Egsmose C, et al. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. *J Rheumatol* 1995;22(12):2208-13.

Why is it important to diagnose and treat RA early?

Trials of treatment strategies

- van der Heide 1996. Recent onset RA, DMARD v placebo
- 12 month study
- The placebo group had higher disability, pain and ESR at 6 and 12 months

van der Heide A, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med 1996;124(8):699-707.

Why is it important to diagnose and treat RA early?

Trials of treatment strategies

- Tsakonas 2000. Early RA - immediate HCQ v 9 month delay
- at 3 years delayed group had worse pain and physical disability

Tsakonas E et al. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. J Rheumatol 2000;27(3):623-9.

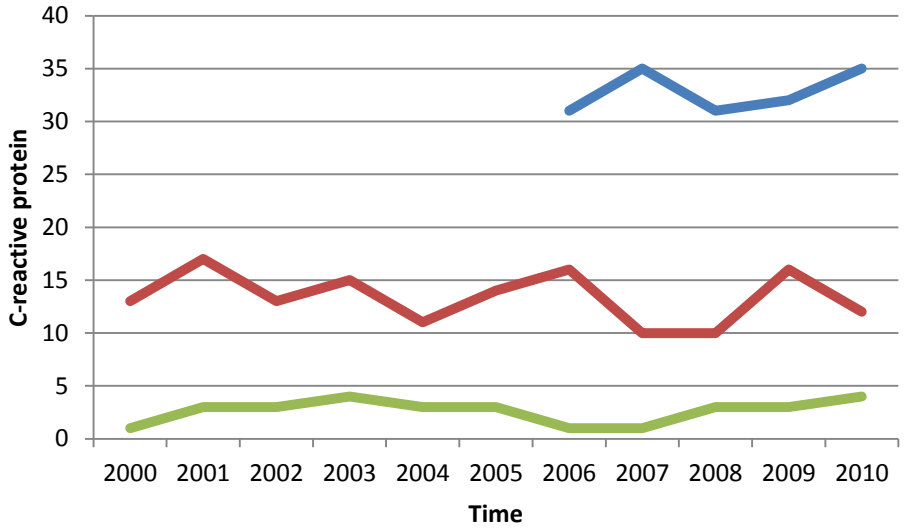
Why is it important to diagnose and treat RA early?

Trials of treatment strategies

- Lard 2001. Recent onset RA, cohort study
- 1993-1995 analgesics then chloroquine / SSZ (mean 123 days)
- 1996-1998 immediate chloroquine / SSZ (mean 15 days)
- early Rx had less radiographic damage at 2 years
- AUC disease activity 64 U in early v 73 U in delayed

Lard LR et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111(6):446-51.

Why is it important to diagnose and treat RA early?



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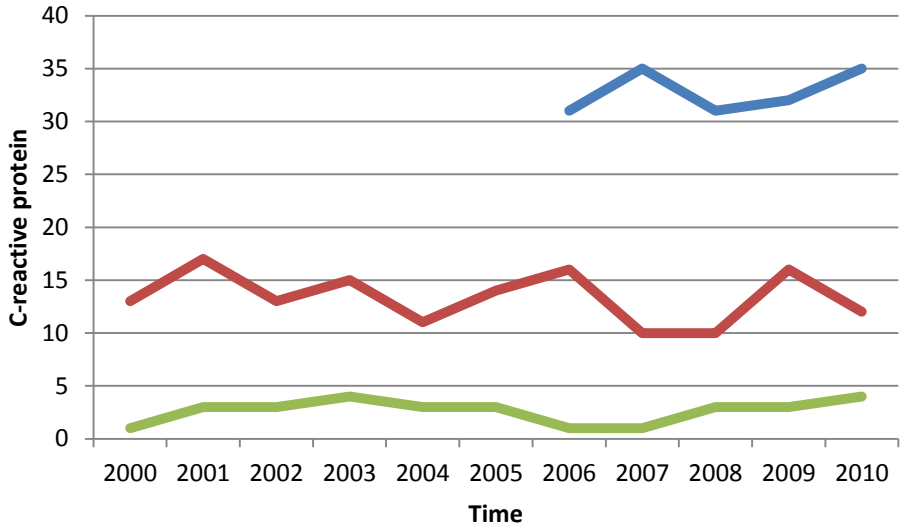

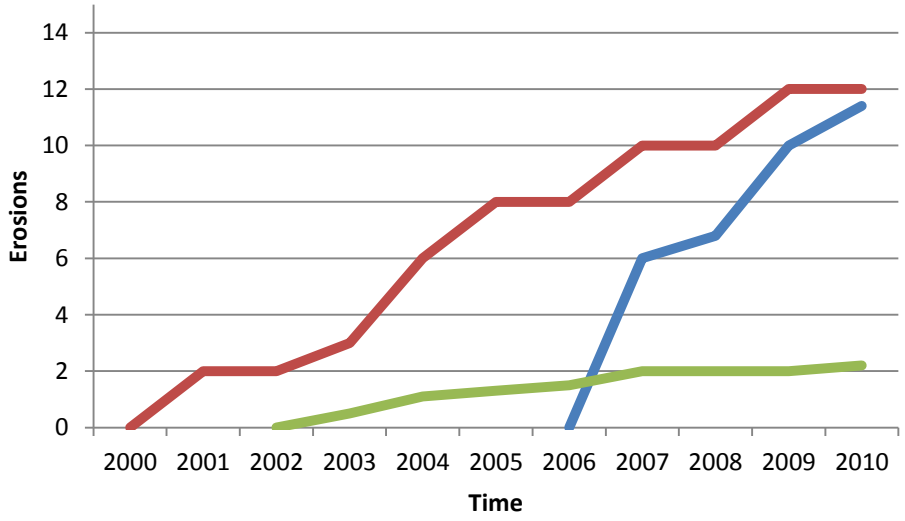

Can we predict prognosis from baseline variables?

Predictors of adverse outcome

- female gender
- insidious onset
- high disease activity
- multiple joints
- baseline erosions
- genetic factors – shared epitope
- serology – RF, anti-CCP

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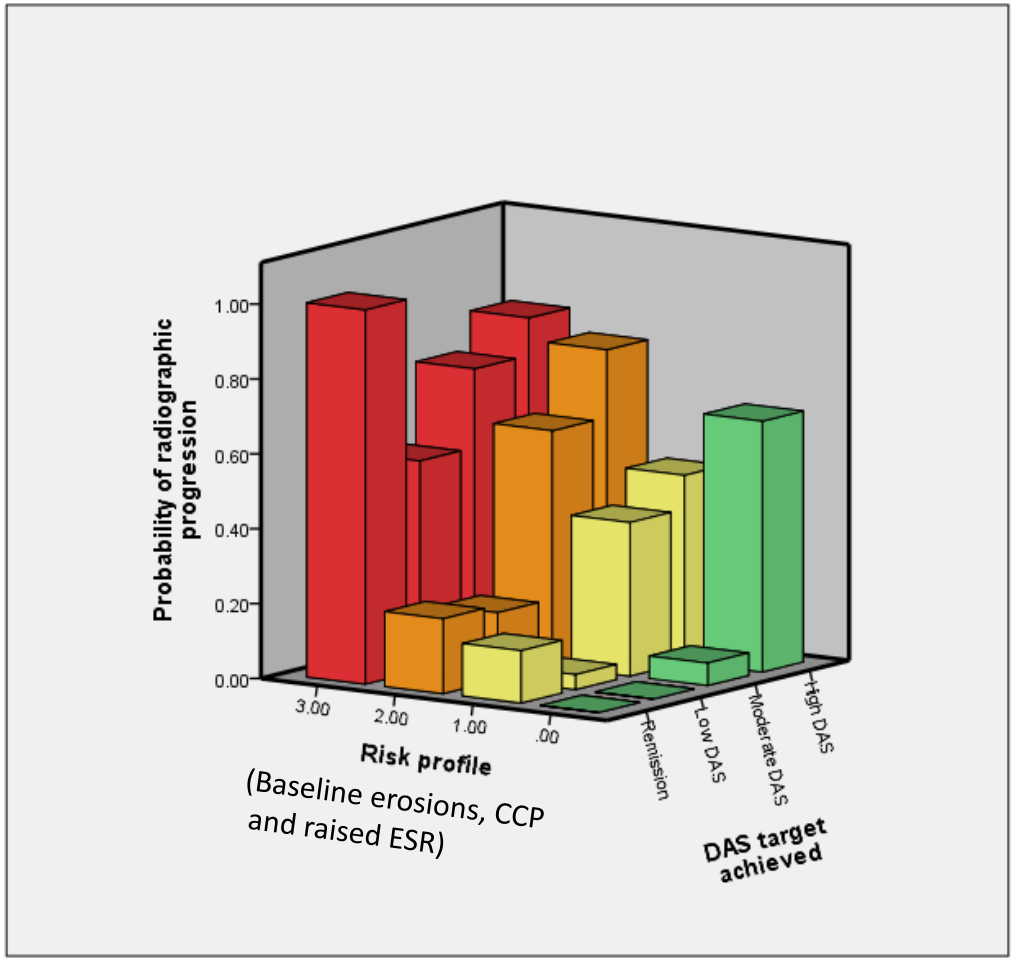
Concept 1: Prognosis is determined by AUC disease activity v time
Influenced by inate (gender, SE) and acquired factors (serology)

Can we predict prognosis from baseline variables?



How low should you go? Towards personalized treatment targets for disease activity in RA. Y. M. R. De Punder 1, T. L. Jansen 1, A. E. van Ede 1, A. A. den Broeder 2, P. L. van Riel 1, J. Fransen 1. 1Rheumatology, Radboud University Nijmegen Medical Centre, 2Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands. EULAR, Madrid, 2013.

Case 1

Amanda, 35 years.
presents with 2 week history of pain, EMS, swelling hands and feet

Diagnoses to consider

- rheumatoid arthritis
- reactive arthritis
- psoriatic arthritis
- viral arthritis
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No diagnosis as yet
How do the principles discussed above inform us?

- the window is wide open but there is some urgency to assess
- predictors of prognosis
    - female gender
    - multiple joints
    - disease activity?
    - serology?
    - erosive status?
    - genetics?

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No diagnosis as yet
How do the principles discussed above inform us?

- the window is wide open but there is some urgency to assess
- predictors of prognosis
    - female gender
    - multiple joints
    - disease activity? (CRP, ESR)
    - serology? (RF, anti-CCP)
    - erosive status? (x-rays hands and feet)
    - genetics? (no need for shared epitope)

Case 1

Amanda, 35 years.
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Other diagnostic indicators

- connective tissue disease (ESR, ANA, ENA, ds-DNA)
- viral arthritis (?Parvovirus B19)
- reactive arthritis (chlamydia, HLA-B27)

Concept 2: The priority in early arthritis is not to make a diagnosis but to manage the risk of the possible diagnoses, especially the bad ones

Case 1

Amanda, 35 years.
presents with 2 week history of pain, EMS, swelling hands and feet

a. Observe (masterly inactivity)
b. Investigate and monitor
c. Investigate and introduce mild treatment (NSAIDs, LD pred, HCQ)
d. Treat intensively

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Urgency determined by the size of the window

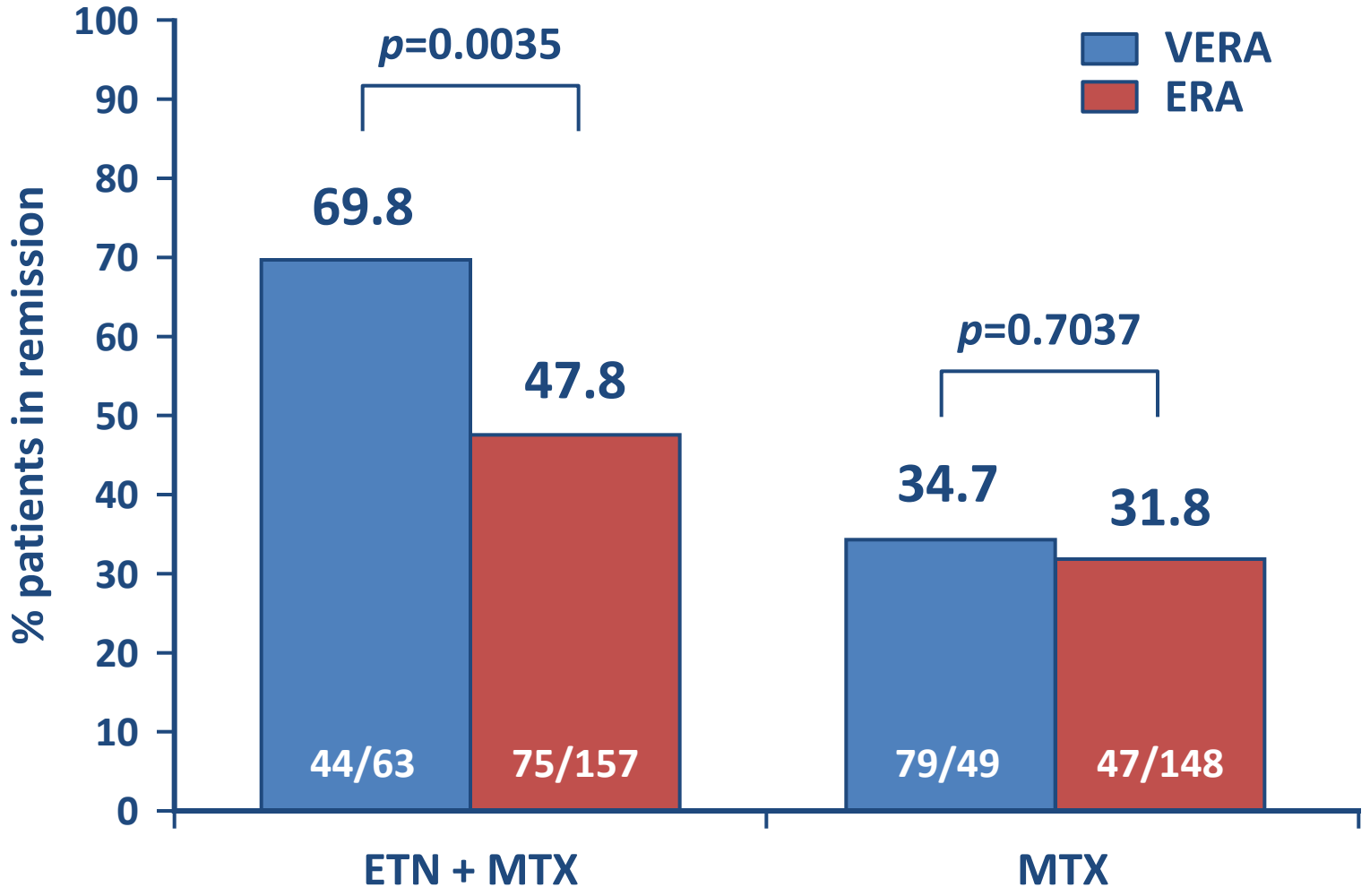
Intensive treatment in early arthritis

COMET study: patients divided into

- VERA <4 months of diagnosis
- ERA 4–24 months
- Primary goal of therapy was remission (DAS28 < 2.6)
- Were remission rates improved by very early treatment with either MTX or MTX and TNFi?
- Assessed at 52 weeks

Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, Singh A, Pedersen RD, Koenig AS, Freundlich B. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008;372(9636):375-82.

Intensive treatment in early arthritis



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Concept 3: RA may be more treatable (?curable) in the very early stages

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Concept 3: RA may be more treatable (?curable) in the very early stages

Should Amanda start DMARDs?

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Results:

CRP	17	ANA 1:40
ESR	32	ENA -ve
RF	26	ds-DNA -ve
anti-CCP > 300		Parvo -ve
x-rays normal		Chlamydia studies -ve

Anti-CCP

Antibodies to citrullinated peptide
Link between genetic and environmental risk factors

	Sensitivity %	Specificity %
RF	75	74
Anti-CCP	68	96

Anti-CCP

Antibodies to citrullinated peptide
Link between genetic and environmental risk factors

Rantapaa-Dahlqvist 2003
Stored sera from 83 RA patients who had been blood donors

	controls %	pre-RA %	early RA %
IgM RF	6.0	19.3	73.1
anti-CCP	1.8	33.7	70.1

Rantapaa-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, Sundin U, van Venrooij WJ. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum* 2003;48(10):2741-9.

Anti-CCP

Antibodies to citrullinated peptide
Link between genetic and environmental risk factors

Rakieh 2013.

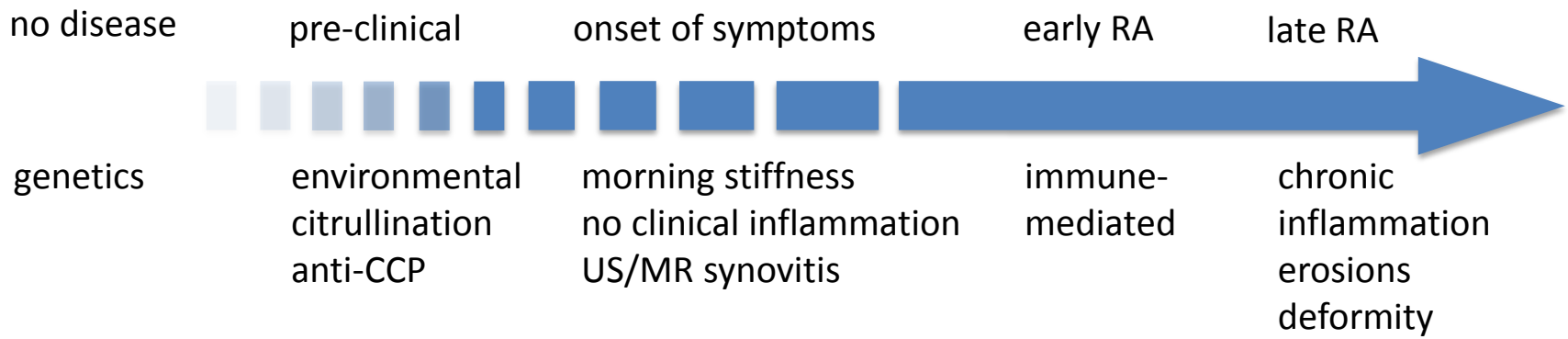
- Screening of patients with non-specific MSk symptoms
- 122 anti-CCP +ve, 22 had clinical synovitis (CS)
- 100 patients followed up
- 44 had developed CS median 26 weeks
- EMS predicted CS (59 min v 19 min)
- Power doppler and MRI were predictive of CS

Rakieh, V. Risk of developing clinical synovitis in ACPA-positive patients with non-specific musculoskeletal symptoms. EULAR, Madrid, 2013.

Anti-CCP

Antibodies to citrullinated peptide
Link between genetic and environmental risk factors

Concept 4: There is a preclinical phase to RA



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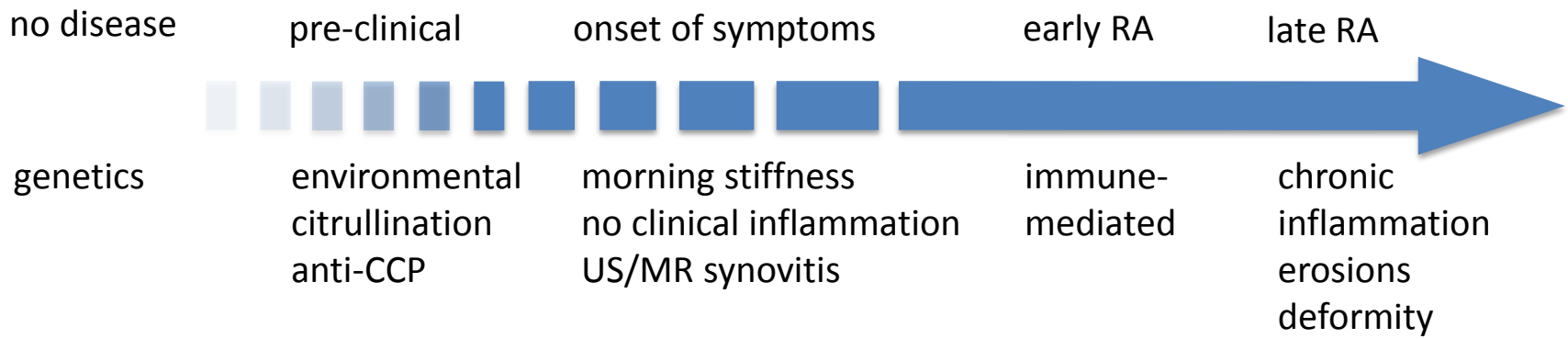

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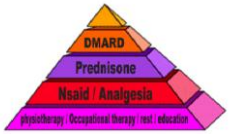

no disease	pre-clinical	onset of symptoms	early RA	late RA
genetics	environmental citrullination anti-CCP	morning stiffness no clinical inflammation US/MR synovitis	immune- mediated	chronic inflammation erosions deformity

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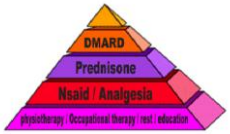

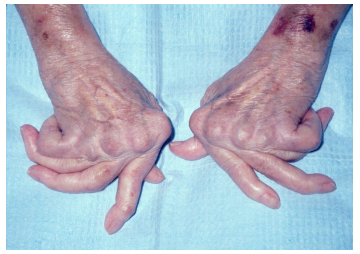

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Where should we intervene?

Case 2

Walter, 42 years, smoker

6 week history of morning stiffness fingers and pain in MTPJs in a.m.

- examination - SJC = 0, +ve MTP squeeze test
- CRP <3, ESR 9, RF –ve, ANA 1:160, urate 0.53

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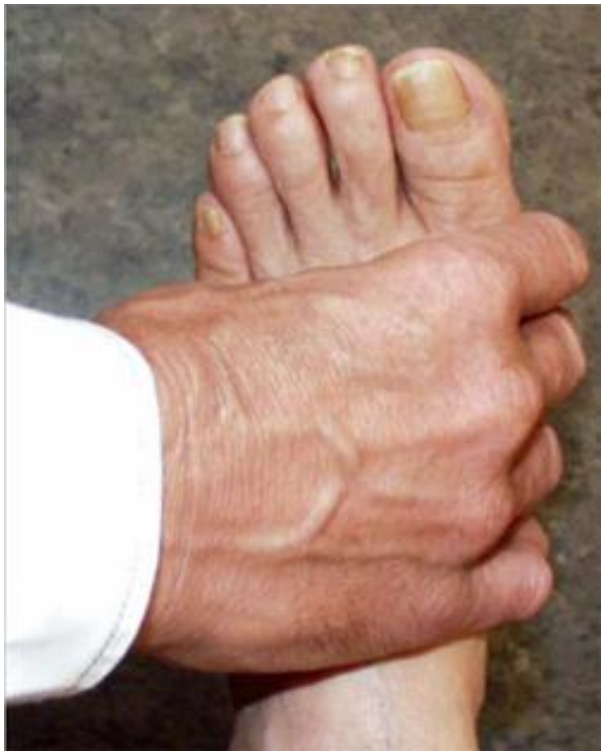

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Other investigations?

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- anti-CCP 162 IU/ml
- x-rays hands and feet normal

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Now what?

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Now what?

a. treat symptoms and wait until synovitis develops
b. start on HCQ
c. prednisone 40 mg / 20 mg / 10 mg over 3/52
d. prednisone plus MTX

What is the evidence for corticosteroids in early RA?

Landewe 2002 COBRA study

SSZ/MTX/Prednisone 60/40/25/20/15/10/7.5 mg v SSZ
By week 56 DMARD use was the same
After 5 years COBRA group had lower DAS28 and fewer erosions

Use of prednisone was considered main factor

Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, van Denderen JC, Westedt ML, Peeters AJ, Dijkmans BA, Jacobs P, Boonen A, van der Heijde DM, van der Linden S. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum* 2002;46(2):347-56.

What is the evidence for corticosteroids in early RA?

Goekoop-Ruiterman 2005 BEsT study

4 strategies in early RA

1. sequential monotherapy DMARDs
2. step-up combination DMARDs
3. initial combination DMARDs plus COBRA prednisone
4. initial MTX/etanercept

Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, Zwinderman AH, Ronday HK, Han KH, Westedt ML, Gerards AH, van Groenendael JH, Lems WF, van Krugten MV, Breedveld FC, Dijkmans BA. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005;52(11):3381-90.

What is the evidence for corticosteroids in early RA?

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4 strategies in early RA

1. sequential monotherapy DMARDs
2. step-up combination DMARDs
3. initial combination DMARDs plus COBRA prednisone
4. initial MTX/etanercept

At 1 year, groups 3 and 4 had less disability than 1 and 2
SvdH scores – 2.0, 2.5, 1.0, 0.5

Initial remission induction with corticosteroid or TNFi improved long term outcome

Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, Zwinderman AH, Ronday HK, Han KH, Westedt ML, Gerards AH, van Groenendael JH, Lems WF, van Krugten MV, Breedveld FC, Dijkmans BA. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005;52(11):3381-90.

abbvie

Breakfast Session

Professor Andrew Harrison

University of Otago
Wellington

Early onset inflammatory arthritis - the clock is ticking - AbbVie Breakfast Session

Sunday, 23 June 2013 Start 7:30am Duration: 60mins Baytrust

Undifferentiated peripheral inflammatory polyarthritis

- consider the differential diagnosis

  - rheumatoid arthritis
  - reactive arthritis
  - osteoarthritis
  - psoriatic arthritis
  - viral arthritis
  - crystal arthritis
  - spondyloarthropathy (undiff, AS)
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Undifferentiated peripheral inflammatory polyarthritis

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Undifferentiated peripheral inflammatory polyarthritis

- consider the differential diagnosis
- rank in order of likelihood
- investigate as appropriate

• rheumatoid arthritis	CRP, RF, anti-CCP, x-rays,
• reactive arthritis	CRP, Chlamydia, HLA-B27
• psoriatic arthritis	CRP, HAL-B27, x-rays
• viral arthritis	CRP, Parvovirus B19
• connective tissue disease	ESR, CRP, ANA, ENA, dsDNA
• spondyloarthropathy (undiff, AS)	CRP,HLA-B27, x-rays,
• sarcoidosis	CRP, CXR, Ca^{++}, serum ACE
• fibromyalgia/pain syndrome	
• systemic autoimmune disease	ESR, CRP, ANA, autoantibodies
• Lyme disease	CRP, Lyme serology
• paraneoplastic	Radiology, tumour markers etc.
• hepatitis	LFTs, hepatitis serology
• endocrine-related	TFTs, ACTH, corticol etc.
~~• osteoarthritis~~	
~~• crystal arthritis~~	
~~• polymyalgia rheumatica~~	

Undifferentiated peripheral inflammatory polyarthritis

If still undifferentiated

- determine risk of adverse prognosis

Clinical

Table 2. Summary of history and physical examination features found to have diagnostic and prognostic value in UPIA.

	Eventual RA Diagnosis	Persistent Disease	Remission	Erosive Disease	Disability
Historical feature					
Older age, yrs	+		+	+	+
Female	+		+ (male)		+
Longer symptom duration		+	+ (shorter duration)		+
Longer/more severe morning stiffness	+	+			
Higher disability at baseline					+
Physical examination feature					
Higher tender joint count	+		+ (fewer joints)		
Higher swollen joint count	+	+		+	
Joint distribution (small/large, upper/lower)	+	+	+ (lack of hand involvement)	+	
MTP compression pain		+		+	
Symmetrical joint involvement	+				
Presence of extraarticular features					+

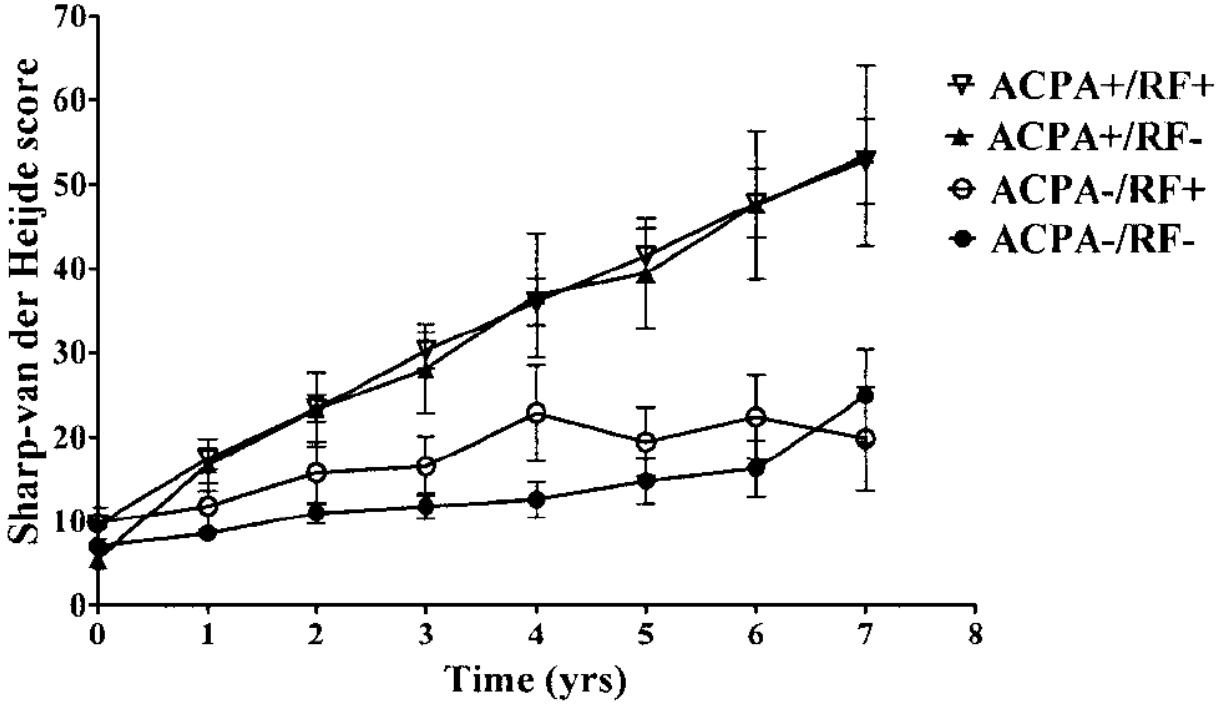
Kuriya B, Villeneuve E, Bombardier C. Diagnostic and prognostic value of history-taking and physical examination in undifferentiated peripheral inflammatory arthritis: a systematic review. *J Rheumatol Suppl* 2011;87:10-4.

Undifferentiated peripheral inflammatory polyarthritis

If still undifferentiated

- determine risk of adverse prognosis

RF and anti-CCP status



van der Linden MP et al. Value of anti-modified citrullinated vimentin and third-generation anti-cyclic citrullinated peptide compared with second-generation anti-cyclic citrullinated peptide and rheumatoid factor in predicting disease outcome in undifferentiated arthritis and rheumatoid arthritis. *Arthritis Rheum* 2009;60(8):2232-41.

Undifferentiated peripheral inflammatory polyarthritis

If still undifferentiated

- determine risk of adverse prognosis

Baseline erosions

Table 2. Likelihood ratios extracted from the different articles on undifferentiated arthritis (UA) and mixed populations.

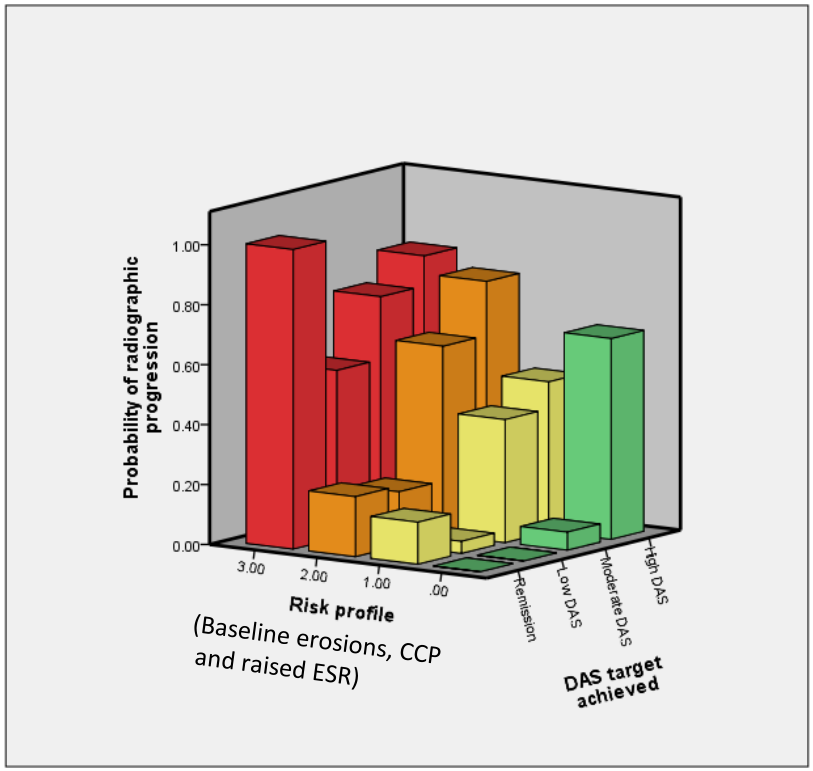
Study	Prognostic Factor	Outcome	LR+ (95% CI)	LR– (95% CI)
UA population				
Van Aken 2005[11]	Erosive disease (SvdH) hands or feet CR	RA (ACR) at 1 year	3.5 (2.1–6.0)	0.8 (0.7–0.9)
Duer 2008[12]	Larsen grade 1 hand or foot CR	RA (ACR) at 2 years	10.9 (1.4–87.3)	0.7 (0.4–1.0)
Mixed population				
Devauchelle 2001[17]	Erosions hands CR	RA according to panel	4.1 (1.7–9.5)	0.9 (0.8–1.0)
Devauchelle 2004[18]	Erosions feet CR	RA according to panel	8.6 (1.9–37.6)	0.8 (0.7–0.9)
	Erosions hands CR		5.7 (1.6–19.8)	0.8 (0.7–1.0)
	Erosions hands and/or feet CR		6.2 (2.4–15.6)	0.7 (0.6–0.9)
Devauchelle 2006[20]	Erosions and/or decalcifications hands CR	RA according to panel	1.8 (1.0–3.1)	0.9 (0.8–1.0)
Saraux 2001[19]	Erosions and/or decalcifications hands CR	RA according to panel	9.7 (3.4–27.2)	0.8 (0.7–0.9)
Gough 1994[21]	Erosions hands or feet CR	Persistent disease*	6.0 (1.9–18.7)	0.7 (0.7–0.9)

Koevoets R, Machado P, Bombardier C, van der Heijde DM. The value of conventional radiographs in undifferentiated arthritis: a systematic review. *J Rheumatol Suppl* 2011;87:26-30.

Undifferentiated peripheral inflammatory polyarthritis

If still undifferentiated

- determine risk of adverse prognosis
- manage to level of risk



How low should you go? Towards personalized treatment targets for disease activity in RA. Y. M. R. De Punder 1, T. L. Jansen 1, A. E. van Ede 1, A. A. den Broeder 2, P. L. van Riel 1, J. Fransen 1. 1Rheumatology, Radboud University Nijmegen Medical Centre, 2Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands. EULAR, Madrid, 2013.

Summary

Concept 1: Prognosis is predicted by AUC disease activity v time
Influenced by inate (gender, SE) and acquired factors (serology)

Concept 2: The priority in early arthritis is not to make a diagnosis but to manage the risk of the possible diagnoses, especially the bad ones

Concept 3: RA may be more treatable (?curable) in the very early stages

Concept 4: There is a preclinical phase to RA

Summary

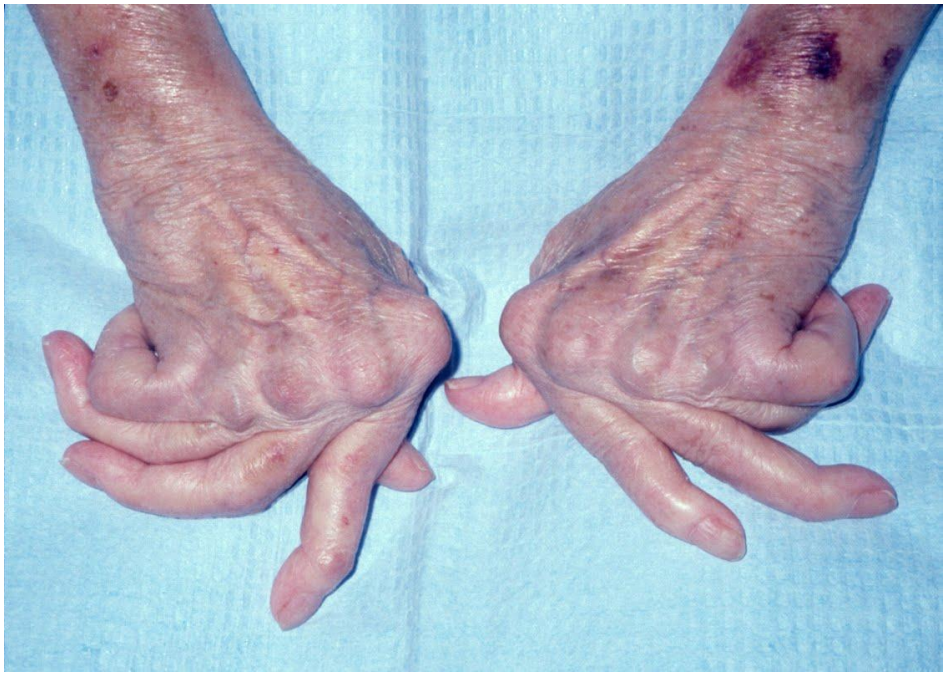
There is a therapeutic window, after which delaying treatment may worsen the long-term outcome

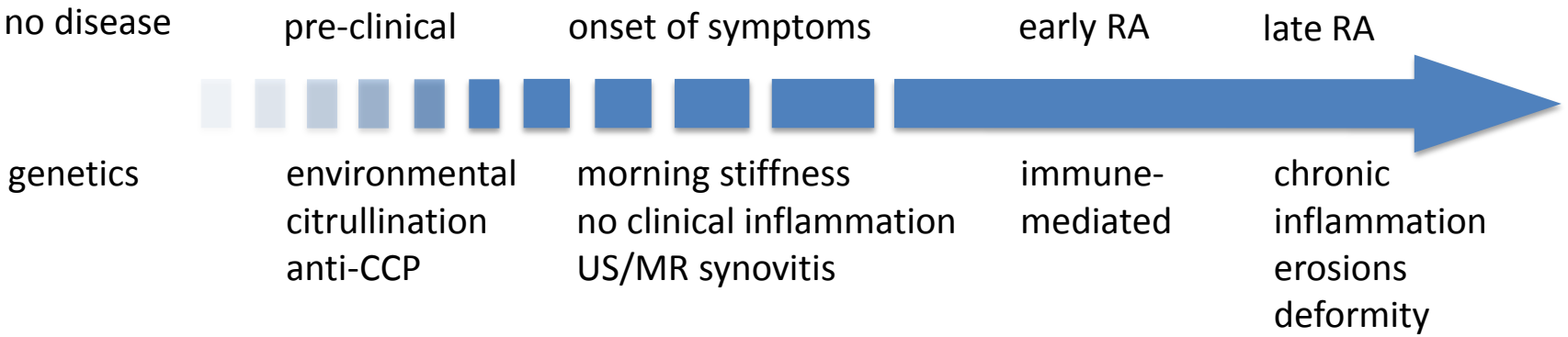
Early remission induction, e.g. with corticosteroids, provides lasting benefit

Even without a diagnosis, baseline variables can be used to determine the urgency and appropriate intensity of treatment

Long-term outcome depends on maintaining remission, with the optimal target being determined by the level of risk

Failure has consequences





Success brings rewards

- outcome of RA is improving

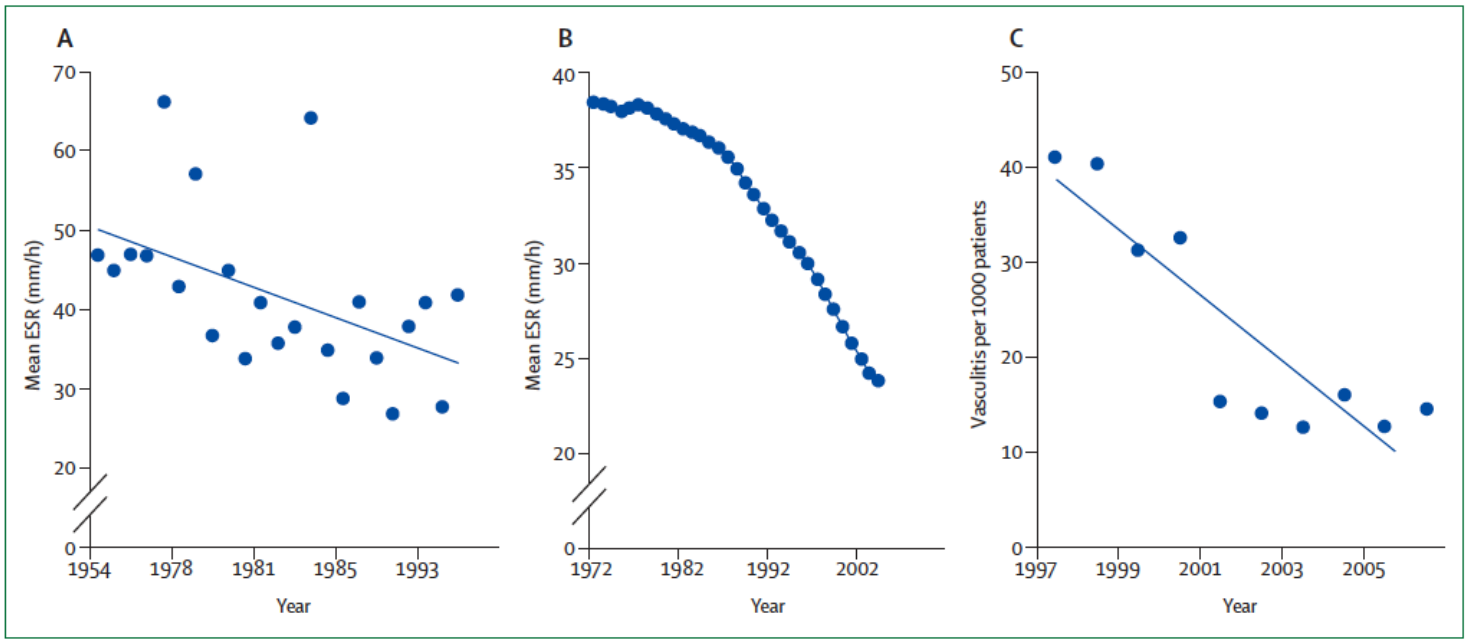


***Figure 3*: Evidence for improvement in rheumatoid arthritis over time**
(A) Mean erythrocyte sedimentation rate (ESR) from international cohort studies (initial mean ESR, by year cohort established).[73] (B) Mean ESR, by year, from US national data bank (previously unpublished analysis of mixed-model regression of 25 343 observations from 2107 patients with rheumatoid arthritis, adjusted for age, sex, education, and follow-up duration). (C) Number of inpatients in the USA with rheumatoid arthritis and vasculitis.[74]

Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010;376(9746):1094-108.