

RISKS IN AUTOIMMUNE ARTHRITIS AND ITS IMMUNOSUPPRESSANT TREATMENT

David A Isenberg
Arthritis Research UK
Professor of
Rheumatology
University College London



1

NUMBERS

BACKGROUND

- 1) Approximately 10 million people in the UK have a musculoskeletal condition
- 2) Amongst the sub-specialities, only psychiatry costs the nation more to look after
- 3) There are approx. 200 different forms of arthritis
- 4) The 3 'big inflammatory ones' are rheumatoid arthritis [RA]; psoriatic arthritis [PA] and ankylosing spondylitis [AS]
- 5) The most lethal is systemic lupus erythematosus [SLE]

2

Rheumatoid Arthritis

- A chronic inflammatory disorder principally affecting the smaller synovial joints in a symmetrical fashion, often leading to joint destruction
- Extra articular manifestations are common
- Strongly associated with rheumatoid factors (RFs)

3

History -1-

- | | |
|-------|--|
| 1400s | Botticelli depicted RA-like deformities in some of his paintings |
| 1800 | Landré Beauvais provided the first good clinical description of RA |
| 1858 | Alfred Baring Garrod first coined the term RA |
| 1897 | Still described juvenile chronic polyarthritis |
| 1924 | Felty linked RA, splenomegaly and leucopenia |

4

History -2-

- **1930s/1940s** Independent description by Waaler (Norway) and Rose (USA) that sheep erythrocytes coated with rabbit serum would agglutinate in the presence of serum from RA patients - led to the development of the RF test.
- **1948/9** Hench and Kendall introduce corticosteroids for RA.
- **1958** The American Rheumatism Association describe first classification scheme for RA.

5

History -3-

- **1960s** John Charnley described first hip replacements
- **1960s/1970s** Immunosuppressive therapy (azathioprine, methotrexate) first used for RA
- **1987** ACR describe revised criteria for RA
- **1994** Introduction of TNF α blockade
- **1998** van Verooij described anti-CCP antibodies; more specific than RF
- **1999 onwards** Introduction of biologic drugs

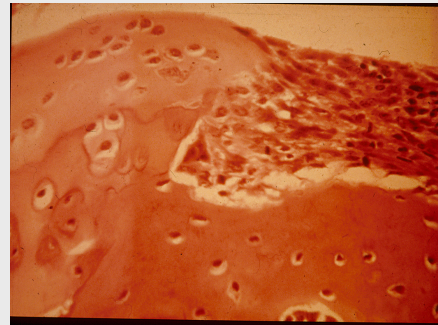
6

ACR Revised Classification Criteria for RA

- 1) Morning stiffness - duration >1hr present for >6 weeks.
- 2) Arthritis in at least 3 areas - present for >6 weeks.
- 3) Arthritis of hand joints - present for >6 weeks.
- 4) Symmetrical nature of arthritis.
- 5) Rheumatoid nodules - observed by a physician.
- 6) Serum rheumatoid factor.
- 7) Radiographic changes - erosions or juxta-articular osteopenia.

7

Pannus Invading Bone



8

Patterns of Disease

- a) Short lived.
- b) Rapidly progressive.
- c) Remission/relapse.
- d) Chronic persistent.
- e) Palindromic.

9

Epidemiology

- 0.5 → 1% in diverse populations worldwide
- Highest in certain North American Indian tribes (Tlinglit, Yakimas, Pimas)
- Lowest in rural African populations
- F:M = 3:1
- Incidence tends to increase in men after 45; in women highest incidence is between 30 and 45

10

Risk Factors

- Female sex (but does oral contraception protect?)
- HLA-DR4
- Smoking
- ?Low level of formal education

11

Joints Involved

- PIPs/MCPs but not DIPs
- Wrists, elbows, shoulders, feet, knees - very common
- TMJ, ankles, hips, C1/C2 cervical spine - less common

12

RA Affecting the Hands -1-



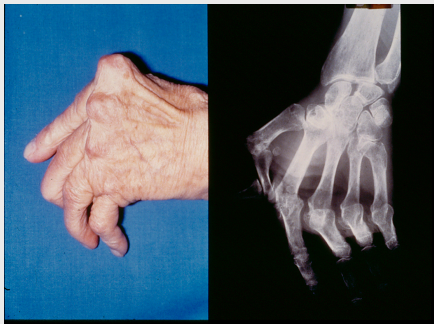
13

RA Affecting the Hands - 2 -



14

Clinical and Radiographic RA Appearances



15

RA is a Multi-System Disease -1-

<p>SKIN Nodules Vasculitis</p>	<p>NERVOUS SYSTEM Entrapment neuropathy Atlanto-axial subluxation Peripheral neuropathy</p>
<p>LUNGS Nodules Interstitial disease Pleural effusion</p>	<p>HEART Nodules Pericarditis ↑Risk of atherosclerosis</p>

16

RA Affecting the Cervical Spine



17

RA is a Multi-System Disease -2-

<p>EYE Sjögren's Scleritis/episcleritis Uveitis</p>	<p>RENAL Amyloidosis Mesangial glomerulonephritis</p>
<p>MUSCLE Muscle weakness - many causes</p>	<p>BONE Osteoporosis</p>

18

Complications

- Increased risk of infection esp. septic arthritis
- Ligament/tendon rupture
- Amyloidosis
- Problems with pregnancy
- Increased risk of atherosclerosis

19

Blood Test Abnormalities

- Haemoglobin often ↓
- ESR/CRP/platelets/alkaline phosphatase often ↑
- IgM RF (70% latex; 90% ELISA)
- IgG RF (65%)
- IgA RF (65%)
- Anti-CCP (90%)

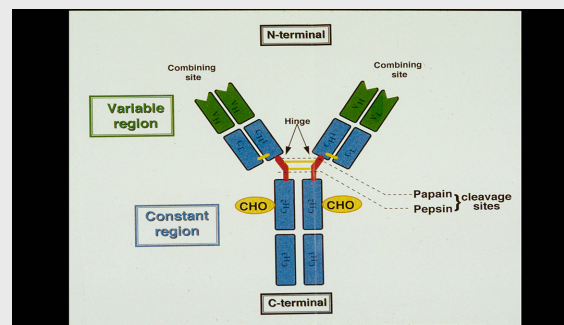
20

Rheumatoid Factor -1-

- A classification criterion
- But low levels may be found in healthy people, especially if >65 years
- May be present in many patients with infection, other autoimmune disease and some cancers
- May be found in individuals many years before they develop the clinical features of RA.

21

Immunoglobulin Structure/Rheumatoid Factor



22

Rheumatoid Factor -2-

	Klebsiella septicaemia (n = 11) %+ve	E.Coli UTI (n = 28) %+ve	Tb (n = 54) %+ve	SLE (n = 48) %+ve	Healthy controls (n = 50) %+ve
IgM RF	20	2	20	50	0
IgA RF	20	2	15	12	0
IgG RF	20	7	42	11	0

Isenberg et al. Clin Exp Immunol 1987; 67: 516

23

Rheumatoid Factor -3-

- High titre IgM-RF in the context of chronic polyarthritis is relatively specific for RA
- High titre IgM-RF is associated with rheumatoid nodules and early erosions
- Aho et al (1991) showed that about one-third of those who developed RA were RF positive up to 4 yrs before disease onset
- RF containing immune complexes may fix complement and act as antigen presenting cells

24

Other Autoantibodies in RA Patients

- approx %
- +ve
- Anti-A2 hn RNP (RA 33) 35
- Anti-perinuclear factor 40-80
- Anti-keratin 50
- Anti-collagen type II 25
- Anti-citrulline containing peptide (CCP) 90

25

Specificity of Anti-CCP

	RF -ve	Anti-RA33 +ve	Anti-CCP +ve
SLE patients			
Deforming major erosions	5/8	6/8	1/8
Deforming minor erosions	1/2	0/2	1/2
Deforming non-erosions	3/6	0/6	0/6
Non-deforming, non erosive	40/215	14/50	1/50

Mediawake et al. Ann Rheum Dis 2001; 60: 67-8

26

Pre-Disease Serology Testing

- Rantapää-Dahlqvist et al studied 83 RA patients who had been blood donors before the disease developed:-

Anti-CCP and IgA RF	Found in 33.7%
IgM RF	Found in 19.3%
IgG RF	Found in 16.9%

- Nb: Serum antibodies were detected 9 years (anti-CCP) to 22 years (RF) before disease onset.

Rantapää-Dahlqvist et al. Arthritis Rheum 2003; 48: 2741-9.

27

NIELSEN ET AL

- 9712 individuals bleed (1981-1983) – part of the Copenhagen City Heart Study and followed for up to 28 years.

- Using multi-variable adjusted hazard ratios for RA development

RF levels	HR	(95% CI)
25 – 50 iu/mL -	3.6	1.7 – 7.3
50 – 100 iu/mL -	6.0	3.4-10
100 iu/ml	26	15-46

The highest absolute risk of RA of 32% was observed in women age 50 – 69, who smoked, with a RF > 100 iu/ml

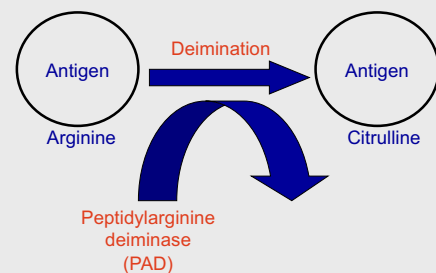
Nielsen et al
Br Med J 2012; 345: 15.

28

Antigenic Targets in RA

- The target of anti-perinuclear factor (Schellekens et al. JCI 1998; 101: 273) and anti-keratin antibodies (Girbal-Neuhauser et al. JI 1999; 162: 585-94) was shown to be a post-translationally modified antigen, filaggrin containing citrulline residues.
- Other studies indicate that citrullinated antigen (e.g. filaggrin, vimentin, fibrin) are physiological candidate target antigens in RA (van Boekel et al Arthritis Res 2002; 4: 87-93).

29



30

'PAD' Locking in RA?

- Can an (unidentified) antigen in the synovium be modified by one or more of the PAD enzymes to create a neopeptide that drives auto reactive T and B cells leading to the clinical manifestations of RA?

• Utz et al. Ann Rheum Dis 2004; 63: 330-2

31

α CCP Status - Longitudinal Analysis

- 279 patients with early RA followed for 5 years
- 57% α CCP at 1st visit (mean 5mn after symptoms)
- **Results**
- α CCP status very stable during 1st 5 yrs of RA
- α CCP +ve predicted a poorer outcome (with greater radiological progression)
- Relatively poor correlation between α CCP and disease activity

• Ronnelid et al. Ann Rheum Dis 2005; 64: 1744-9

32

α CCP + Extra-Articular Disease (ExAD)

- 35 consecutive patients with severe extra articular disease matched with 70 disease controls

	<u>ExAD</u>	<u>No-ExAD</u>	<u>pvalue</u>
• α CCP	77%	56%	0.03
• RF	94%	71%	0.006

- Thus correlation with extra articular disease is stronger for RF than for α CCP.

Turesson C et al. Ann Rheum Dis 2007; 66: 59-64

33

Citrullination - Physiological Importance

- **Citrullination is essential for:-**
- The generation of structural tissues such as the skin as an impermeable membrane
- The assembly of the myelin sheath as an electrical insulator of the nerve trunk or axon
- The function of histones as support structures and transcriptional control elements for DNA

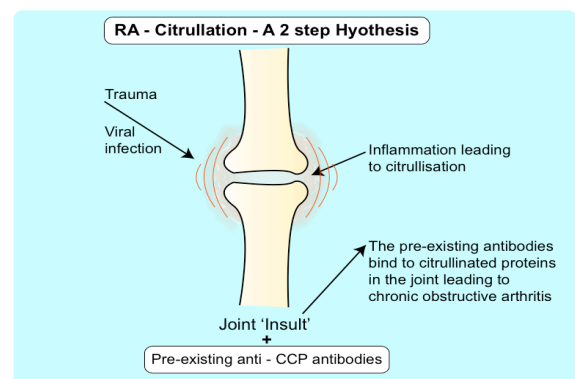
34

RA and Citrullination - A 2 Step Hypothesis -1-

- There is no evidence that the immune response to citrullinated proteins can induce synovitis
- Anti-CCP antibodies can 'appear' in the blood up to a decade before RA is diagnosable
- Citrullinated proteins are absent in the healthy joint

35

RA and Citrullination - A 2 Step Hypothesis -2-



36

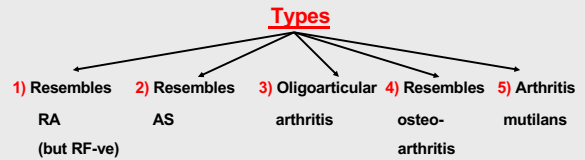
Conclusions

- RA remains a potentially serious autoimmune rheumatic disease affecting around 400,000 people in the UK
- An increased understanding of its immunopathology has led to more targeted therapies e.g. anti-TNF alpha drugs
- Although rheumatoid factor is invariably tested anti-CCP antibodies have provided an additional and more specific antibody test
- Citrullination has emerged as an important physiological process which if 'subverted' may have a role in the development of RA

37

PSORIATIC ARTHRITIS (1)

- Psoriasis – a common skin disease
- Maybe 10-25% of psoriasis patients have arthritis



38

PSORIATIC ARTHRITIS (2)

KEY FEATURES

- Prevalence ranges from 0.04% - 1.2%
- Nail dystrophy, enthesitis and dactylitis are common
- Rheumatoid factor is usually absent
- nb the psoriasis may be restricted to the scalp or natal cleft

39

ANKYLOSING SPONDYLITIS (1)

KEY FEATURES

- Insidious onset usually < 40 years
- Prevalence estimates vary from 0.1% - 1.4%
- M:F \cong 2:1
- Presents with low back pain, marked early morning stiffness
- Strong association with HLA-B27

40

ANKYLOSING SPONDYLITIS (2)

KEY FEATURES

- Uveitis is common accompaniment
- Bilateral features (n.b. sacroiliitis)
- Untreated, it leads to limited motion of the lumbar spine and limited chest expansion
- Exercise is beneficial
- The primary pathological site is the enthesis (insertion of the ligaments and capsules into bone): later fibrosis and ossification develop

41

TREATMENTS – OLD, NEWISH, NEW (1)

1897 – 1948	Aspirin Gold Salazopyrine						
1948 – 1995	<table border="0"> <tr> <td>Steroids</td> <td>Hydroxychloroquine</td> </tr> <tr> <td>Azathioprine</td> <td>Cyclosporine</td> </tr> <tr> <td>Methotrexate</td> <td>Cyclophosphamide</td> </tr> </table>	Steroids	Hydroxychloroquine	Azathioprine	Cyclosporine	Methotrexate	Cyclophosphamide
Steroids	Hydroxychloroquine						
Azathioprine	Cyclosporine						
Methotrexate	Cyclophosphamide						
1995 – Now	Combinations of the above Mycophenolate Tacrolimus + 'The Rise of The Biologics'						

42

TREATMENTS – OLD, NEWISH, NEW (2)

Treatment of RA/Psoriatic Arthritis

STANDARD: 'Triple Therapy'

Hydroxychloroquine
Salazopyrine
Methotrexate
+/- low dose steroids

- Effective in approx. 60% of patients

43

THE RISE OF THE BIOLOGICS (1)

Treatment of RA/Psor Arthritis/Ank Spond for patients in whom conventional therapy does not work

Antibodies to:-

- TNF α (5 types – e.g. Enbrel, Humira)
- IL6R (IL6) – Tocilizumab
- CD20 – e.g. Rituximab

Abatacept [blocks the link between the antigen-presenting cell and the T-cell]

JAK-STAT inhibitors

44

THE RISE OF THE BIOLOGICS (2)

And the 'new kids on the block'

Anti-IL-17(A) – Secukinumab used for PA and AS

Anti-IL-12/23 – Ustekinumab used for psoriasis/PA and under investigation in SLE

45

MONITORING AND SAFETY AT SEA! – 1-

1. Hydroxychloroquine – no blood monitoring
2. Salazopyrine – FBC/U & E/LFTs every three months approximately
3. Methotrexate – FBC/U & E/LFTs every six weeks approximately
4. Biologic drugs – FBC/U & E/LFTs every one to two months approximately
5. Steroids – formal blood monitoring not usually required but be mindful of increased infection risk, high blood pressure, osteoporosis and diabetes.

46

MONITORING AND SAFETY AT SEA! – 2-

6. It is not advisable to go to sea for a lengthy period having just started an immunosuppressive or biologic drug.
7. The biologic drugs are associated with an increased risk of infection in the first three to six months.
8. The safe dose of steroids is about 6mg per day.

47