Autoimmune disease: diagnosis, treatment, cardiovascular disease, and mortality

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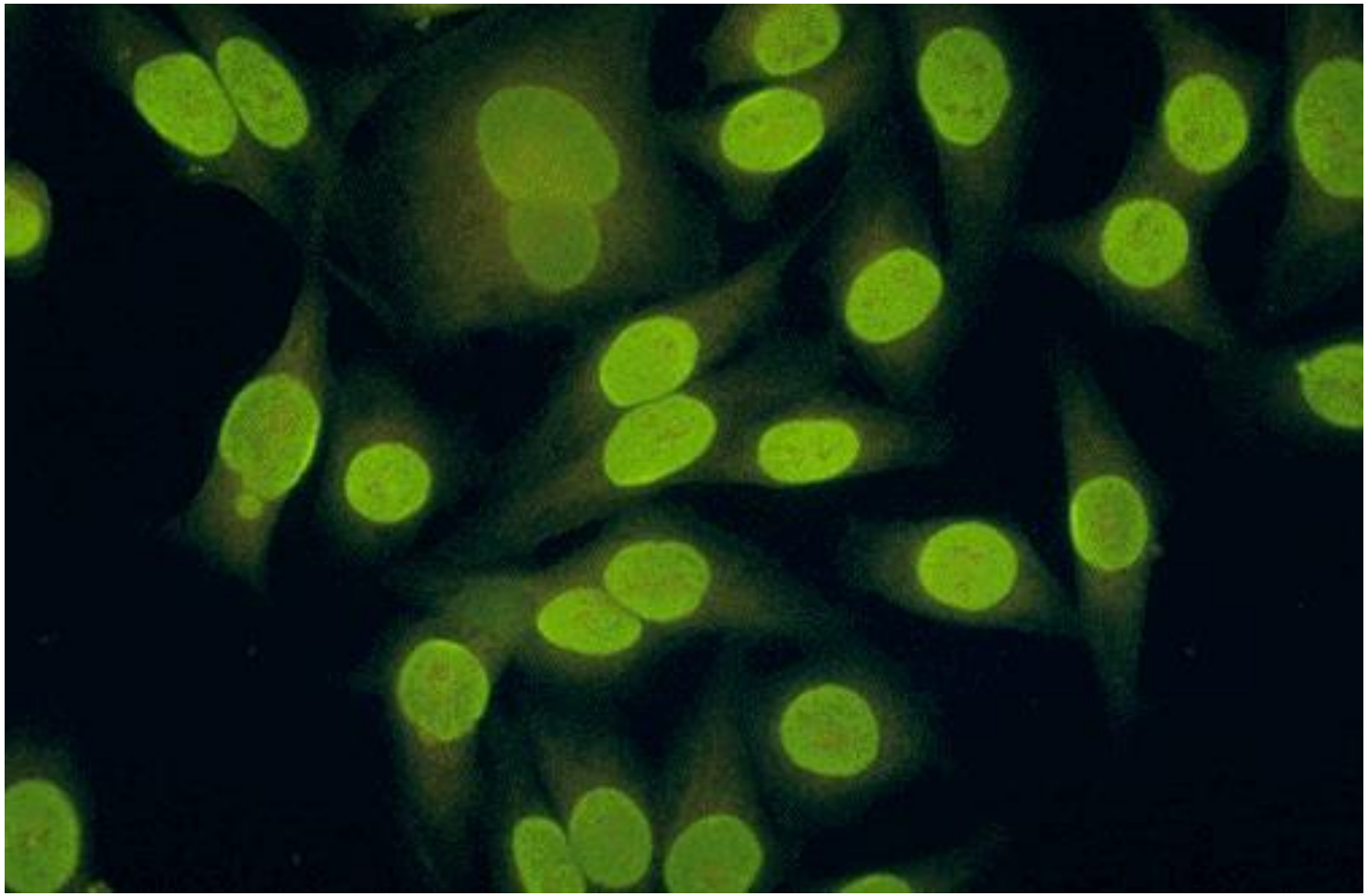
Objectives

- Serologies in autoimmune disease
- Newer biologics for connective tissue diseases
- Connective tissue disease as risk factor for atherosclerotic disease
- Predictors of mortality in CTD

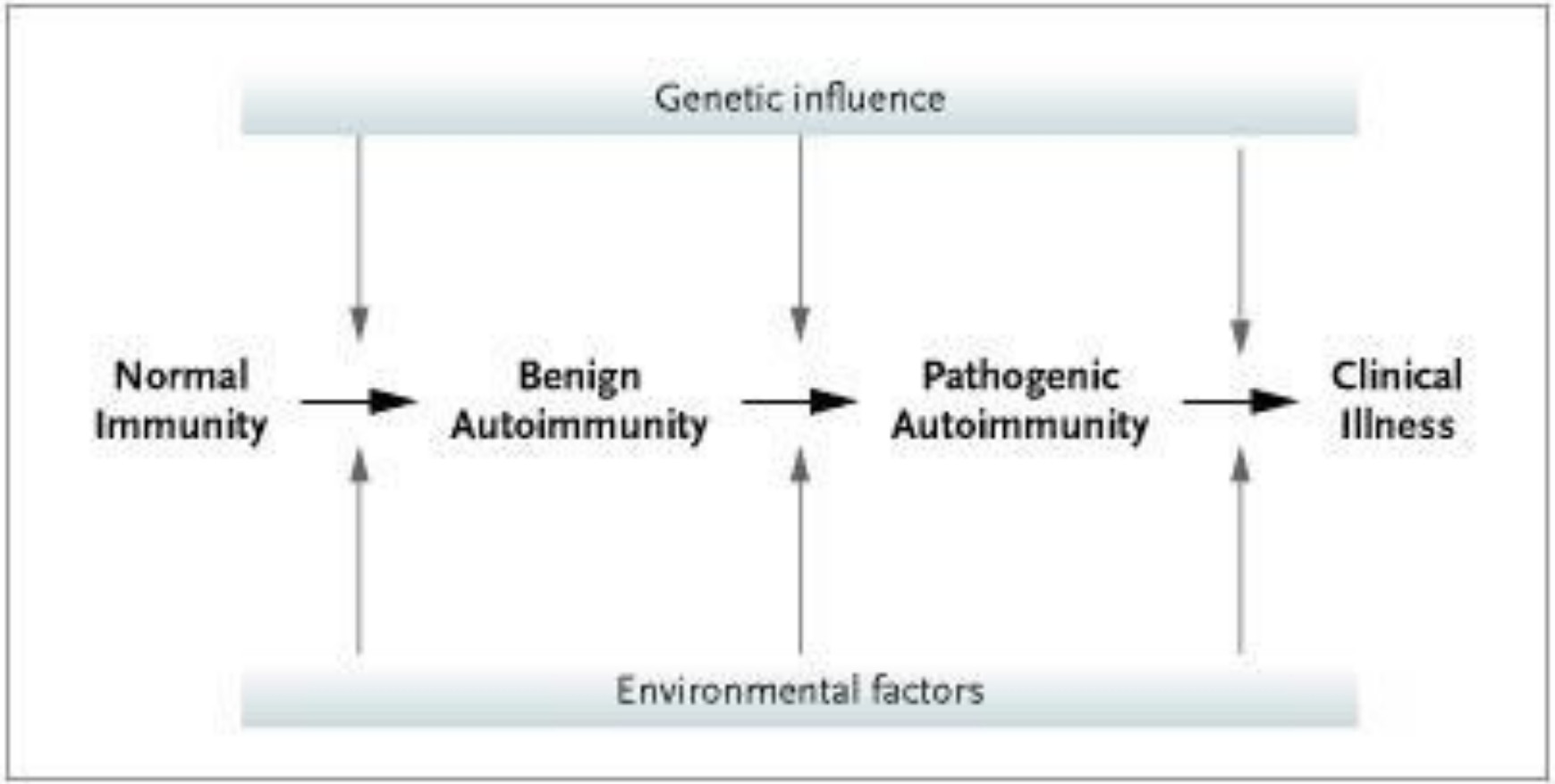
Antinuclear Antibody

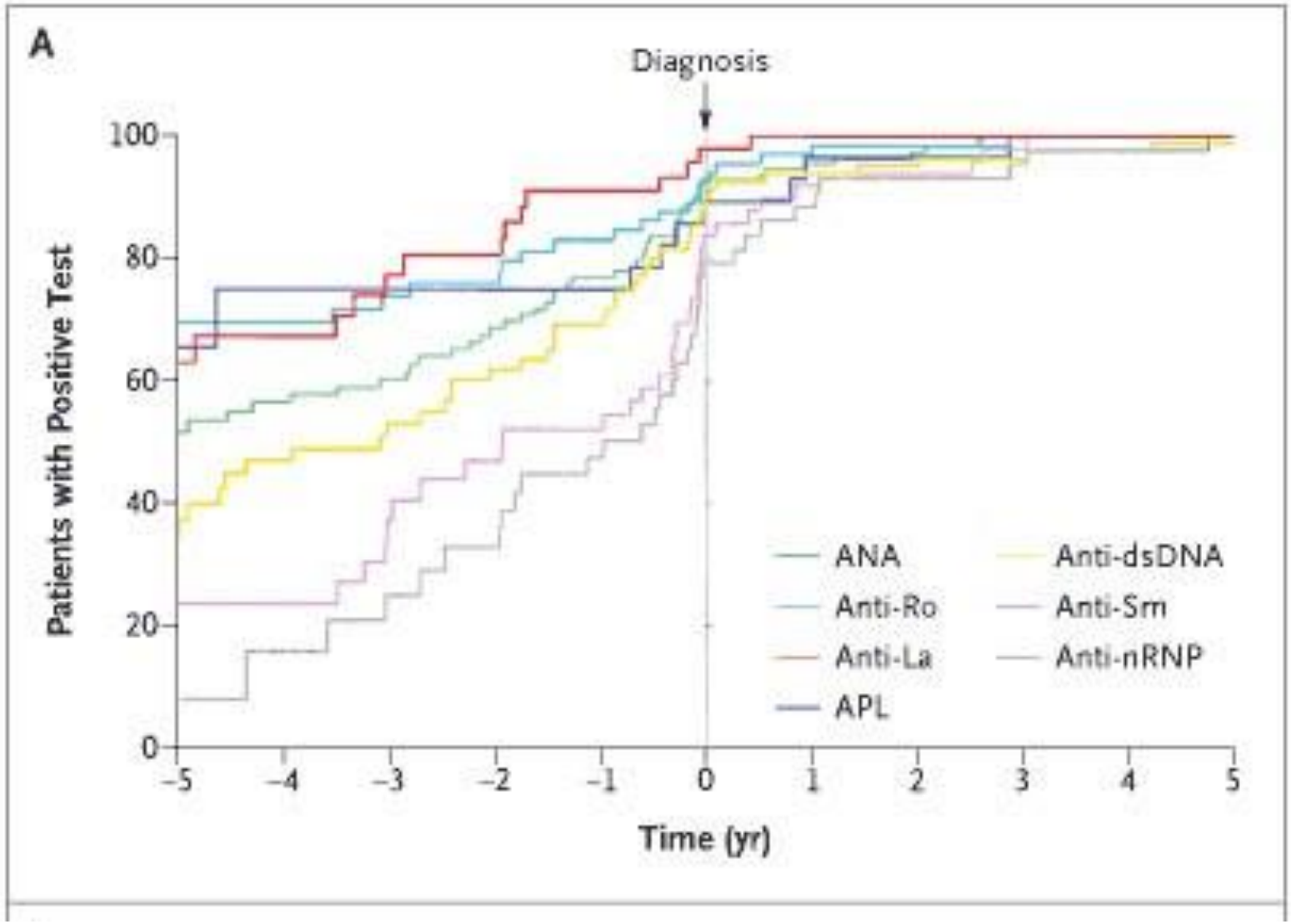


ANA testing

- 98% sensitive
- 95% specific at 1:160
- 20% of 1st degree relatives of SLE patients will be ANA positive, while only 5% will get SLE
- The prevalence of ANA increases with aging and infections

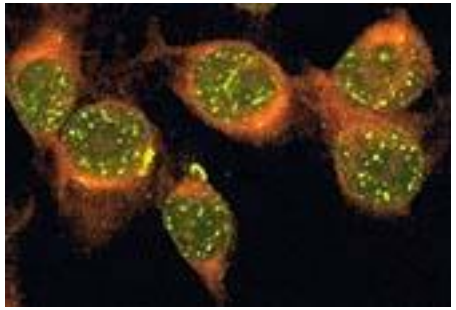
Progression to clinical autoimmunity



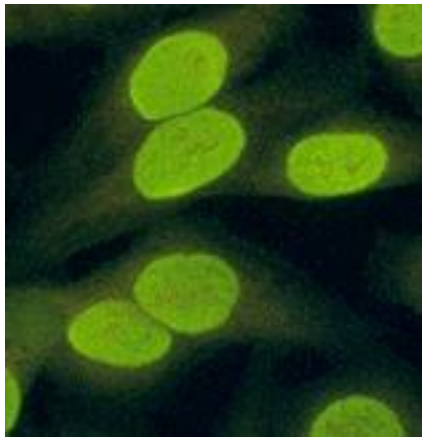


Arbuckle MR et al. N Engl J Med 2003;349:1526-1533.

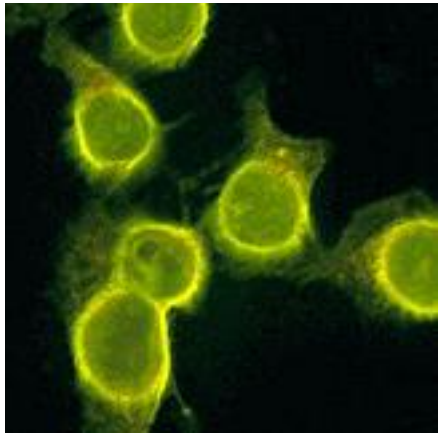
ANA patterns



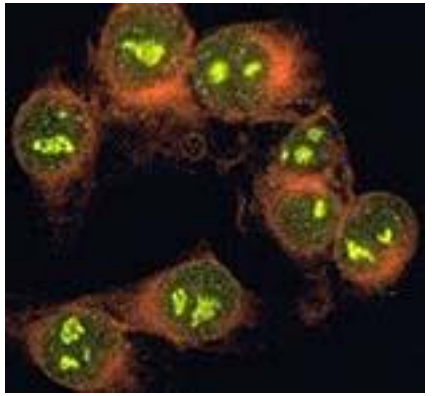
speckled



homogeneous

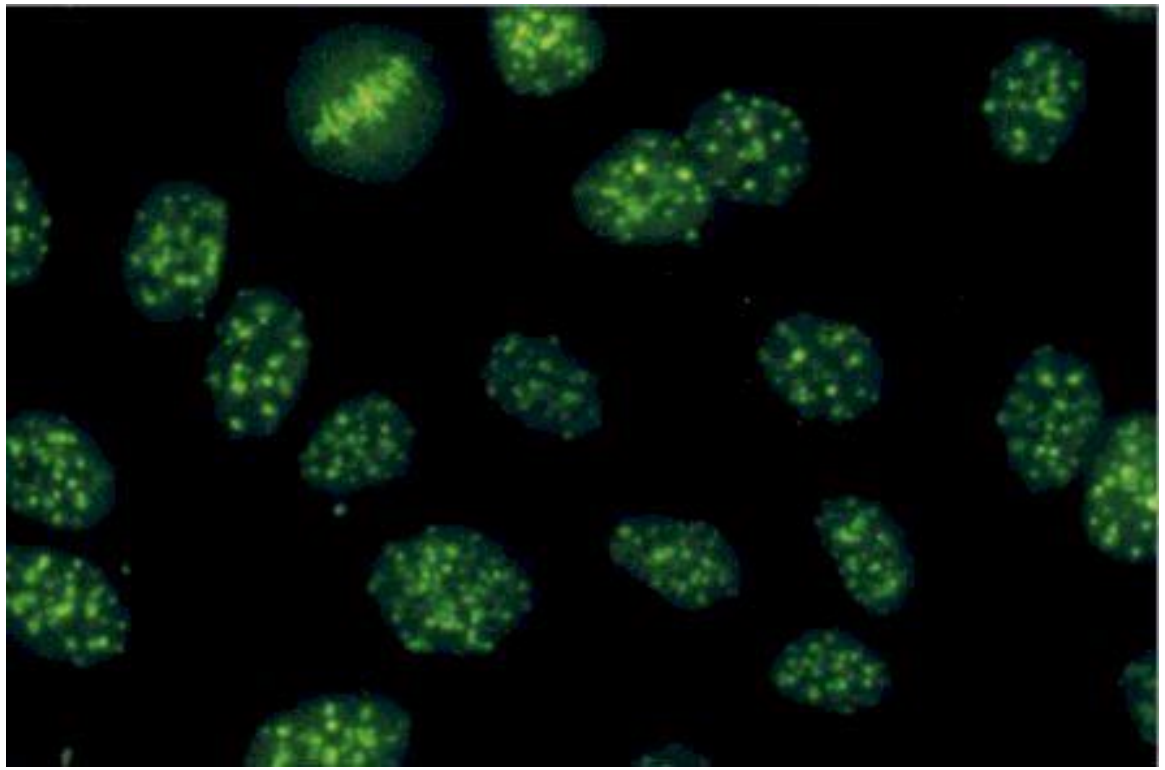


rim



nucleolar

Centromere

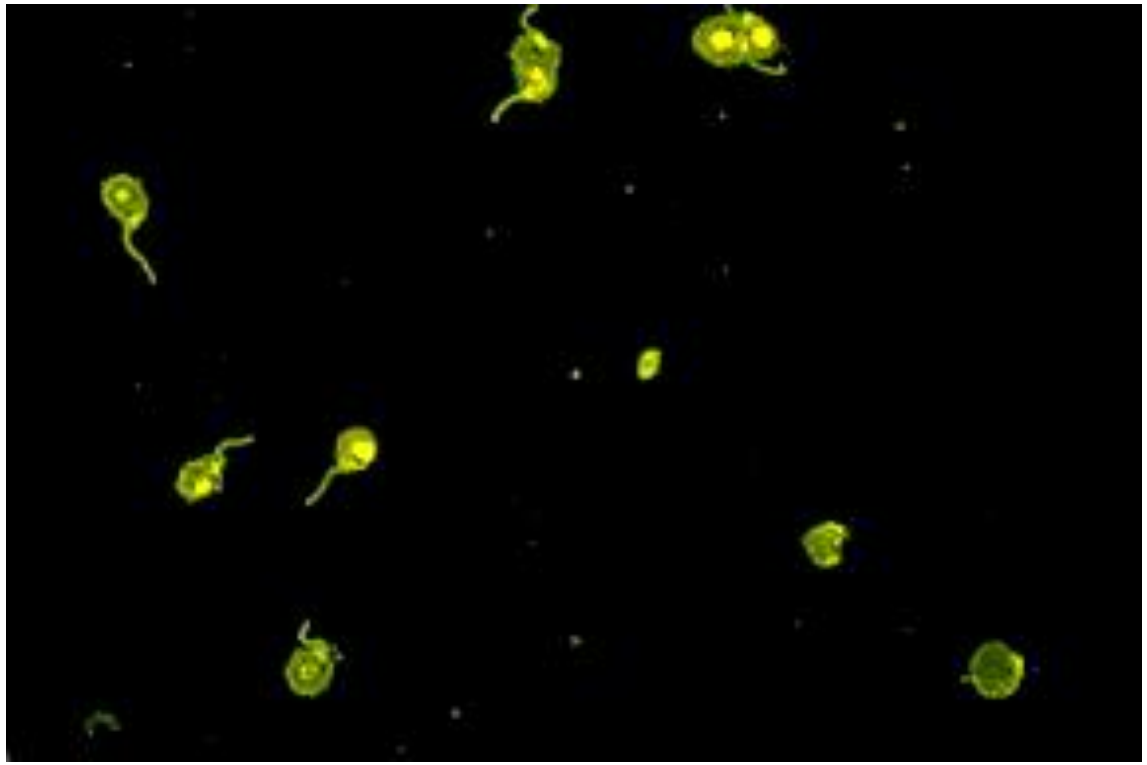


What do the patterns mean?

- Speckled - Seen in lupus, overlap syndromes
- Rim - dsDNA. Specific for SLE.
- Homogenous - Seen in drug-induced lupus.
- Nucleolar - Seen in scleroderma
- Centromere - Seen in CREST syndrome

Extractable Nuclear Antigens (ENA) and autoantibodies

- Anti-Smith, Ro, La, RNP, Scl-70 antibodies
- anti-double stranded DNA antibodies
- lupus anti-coagulant/ anti-cardiolipin antibodies



ENA (extractable nuclear antigen) antibodies

- Smith – specific to SLE, 25% sensitive
- Ro (SSA) – 30% sensitive, seen in Sjögren's syndrome (50%), neonatal lupus, congenital heart block, subacute cutaneous lupus
- La (SSB) - 10% of SLE, more specific for Sjögren's
- RNP – 30-40% of SLE; in isolation seen in overlap syndromes with scleroderma, rheumatoid arthritis, and myositis
- Scl-70 – 30% sensitive, 95% specific for scleroderma

Take Home Points

- Lupus is a clinical not a laboratory diagnosis
- Treat what you see
  - Prevent damage
  - Improve quality of life

Serologies in RA

- Rheumatoid Factor (RF)
  - Positive test in ~75% of patients with RA
  - Occasionally occurs in other inflammatory diseases (Hepatitis C, TB, chronic infections)
  - Also seen in 5% of the population
  - Associates with erosions, damage, nodules, pulmonary fibrosis
- Anti-CCP antibodies
  - Anti-cyclic citrullinated peptide antibodies
  - Highly specific for RA (90%)
  - Correlates well with disease progression (erosions, systemic features)

Markers of inflammation

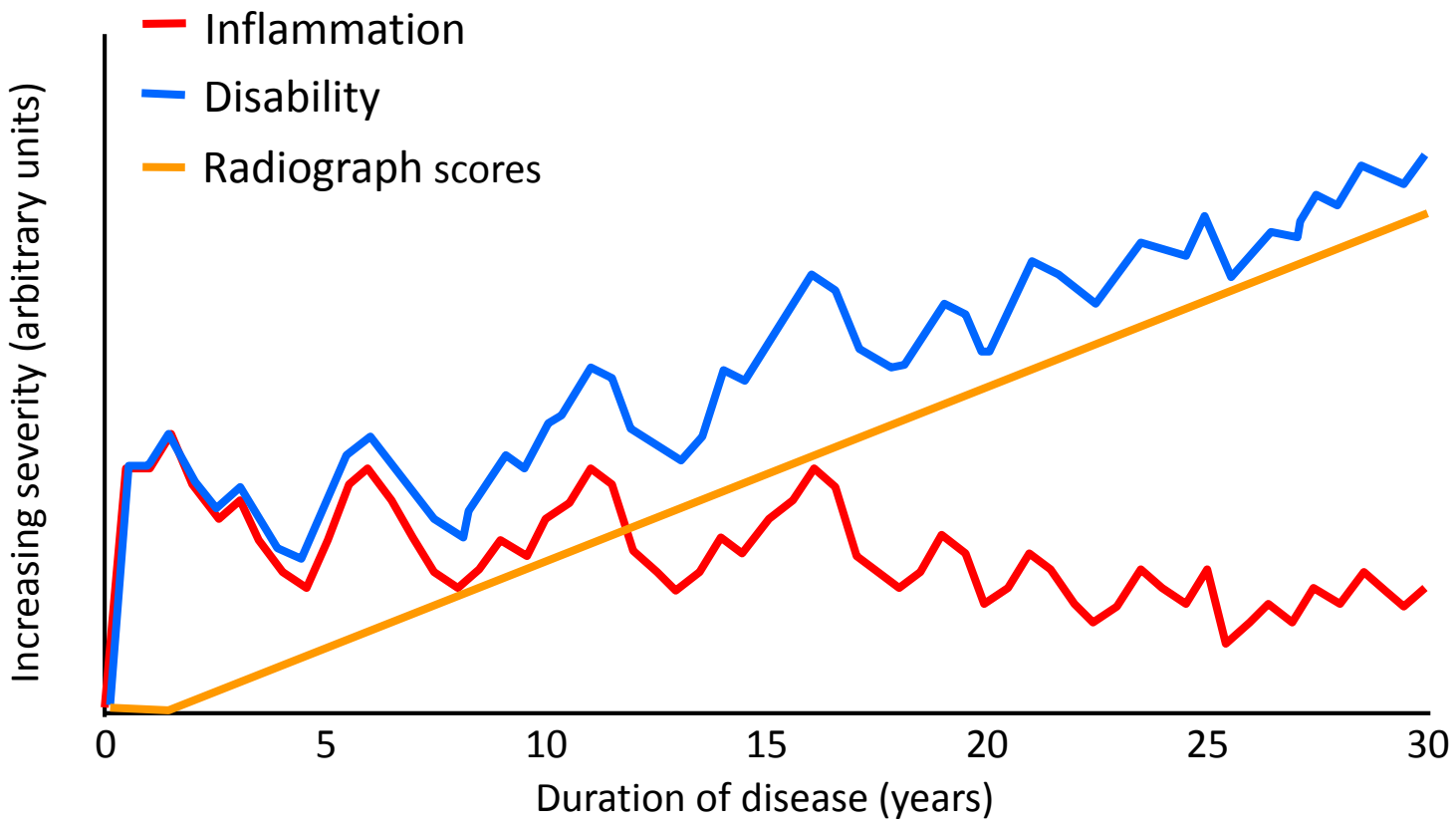
- Erythrocyte sedimentation rate (ESR)
  - Measures how rapidly red blood cells settle
  - Useful to monitor disease course
- C-reactive protein (CRP)
  - Serum protein that increases rapidly after tissue injury, indicating acute inflammation (typically >0.7 mg/dL)
  - May be used to monitor disease course

90% of the joints involved in RA are affected within the first year

SO TREAT IT EARLY

Relationship of Radiographic Joint Damage to Disability

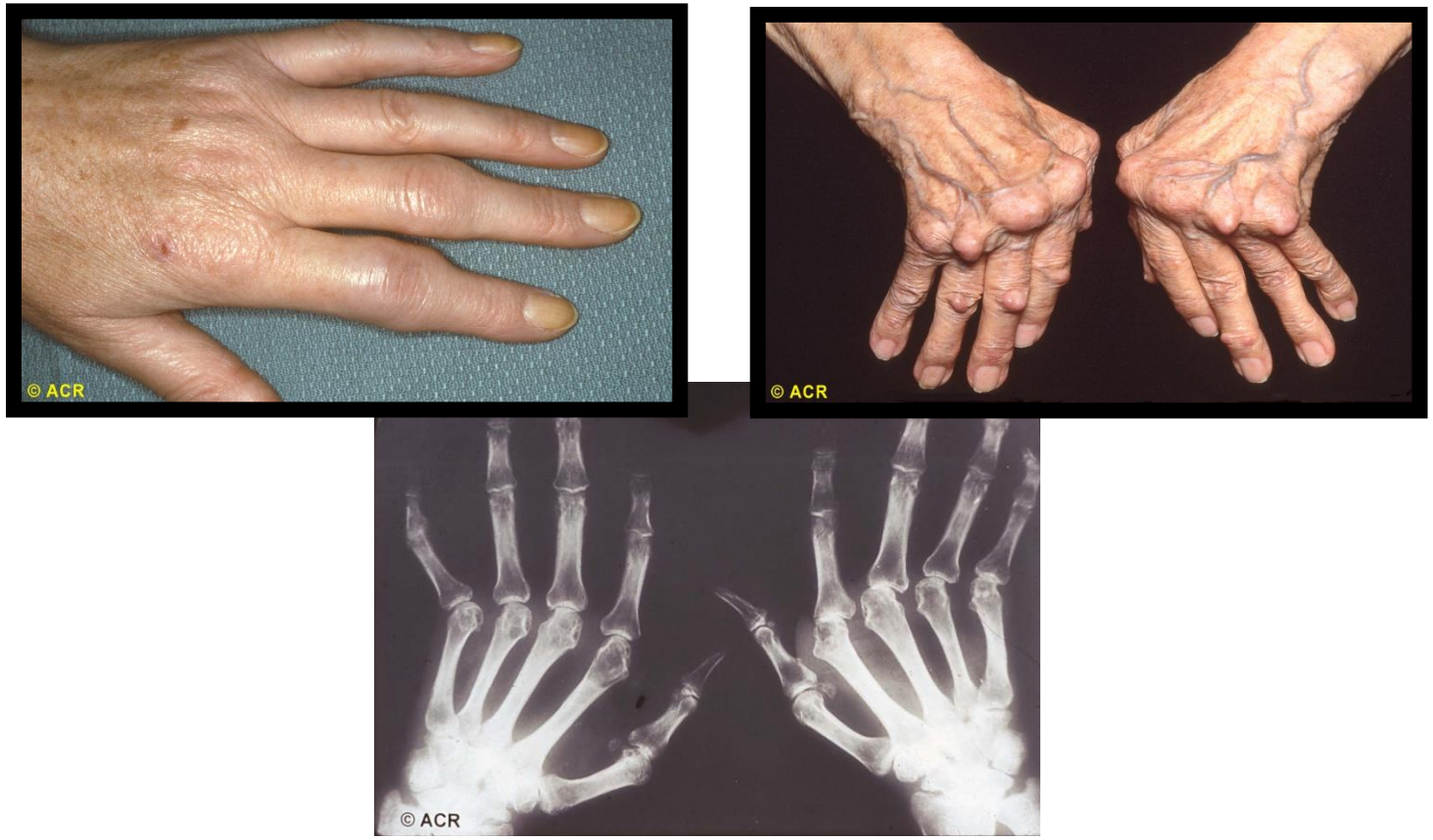
Model of joint disease progression



Kirwan JR. *J Rheumatol* 2001;28:881-6.

Please see accompanying full prescribing information.

Clinical and Radiographic Symptoms of RA



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Please see accompanying full prescribing information.

Drugs for RA

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Disease-modifying anti-rheumatic drugs (DMARDs)
  - Synthetic
  - Biologic
- Glucocorticoids

DMARDs

Disease Modifying Anti-Rheumatic Drugs

- Reduce swelling & inflammation
- Improve pain
- Improve function
- Have been shown to reduce radiographic progression (erosions)

Synthetic DMARDs (traditional)

- Methotrexate
- Sulfasalazine
- Hydroxychloroquine
- Leflunomide
- Azathioprine

Common DMARD Combinations

- Triple Therapy
  - Methotrexate, Sulfasalazine, Hydroxychloroquine
- Double Therapy
  - Methotrexate & Leflunomide
  - Methotrexate & Sulfasalazine
  - Methotrexate & Hydroxychloroquine
  - Sulfasalazine & Hydroxychloroquine

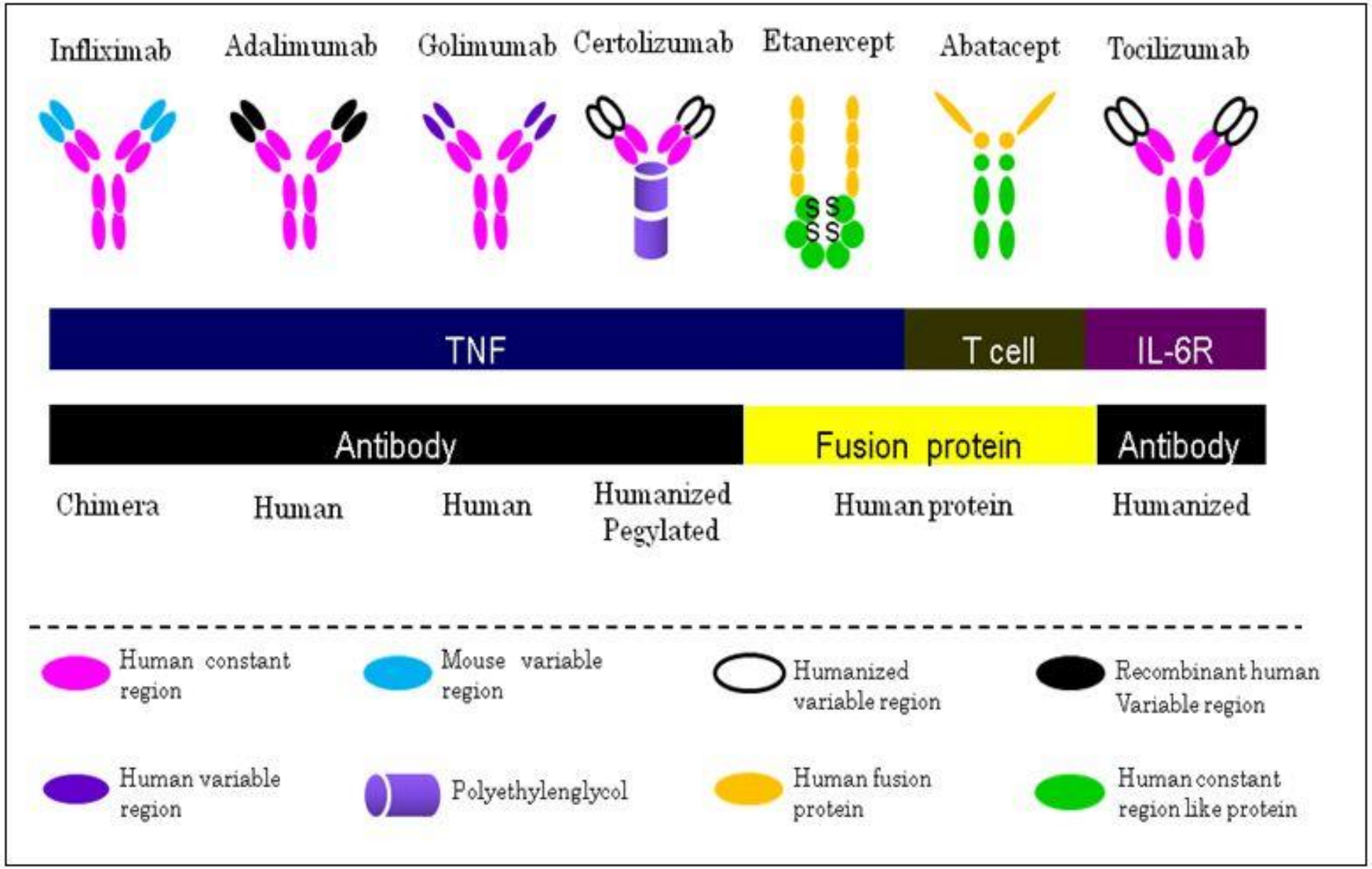
Biologic Therapy

- Complex protein molecules
- Created using molecular biology methods
- Produced in prokaryotic or eukaryotic cell cultures
- Naming
  - “imab” = chimeric monoclonal (has mouse bits)
  - “umab” = humanized monoclonal
  - “cept” = fusion protein with Fc receptor

Concerns in biologic therapy

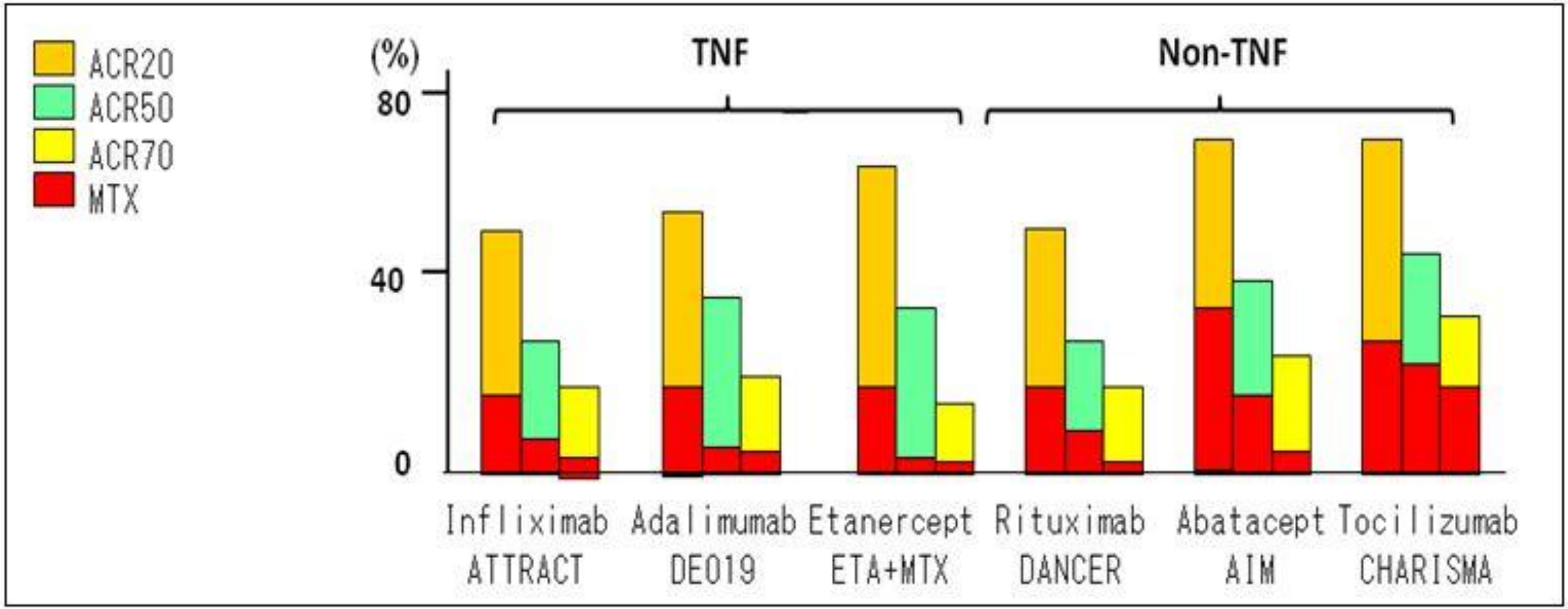
- Slight increased risk for infection vs. placebo
- However, reduces over time due to replacement of prednisone
  - RR from 4.8 to 2.2 over 3 years
  - RR prednisone 7.5–14 mg/day, IRR_{adj} 2.1
  - Prednisone ≥15 mg/day, IRR_{adj} 4.7
  - TNFα inhibitors IRR_{adj} 1.8

Ann Rheum Dis. 2011 Nov 1; 70(11): 1914–1920.



DOI: 10.5772/53321

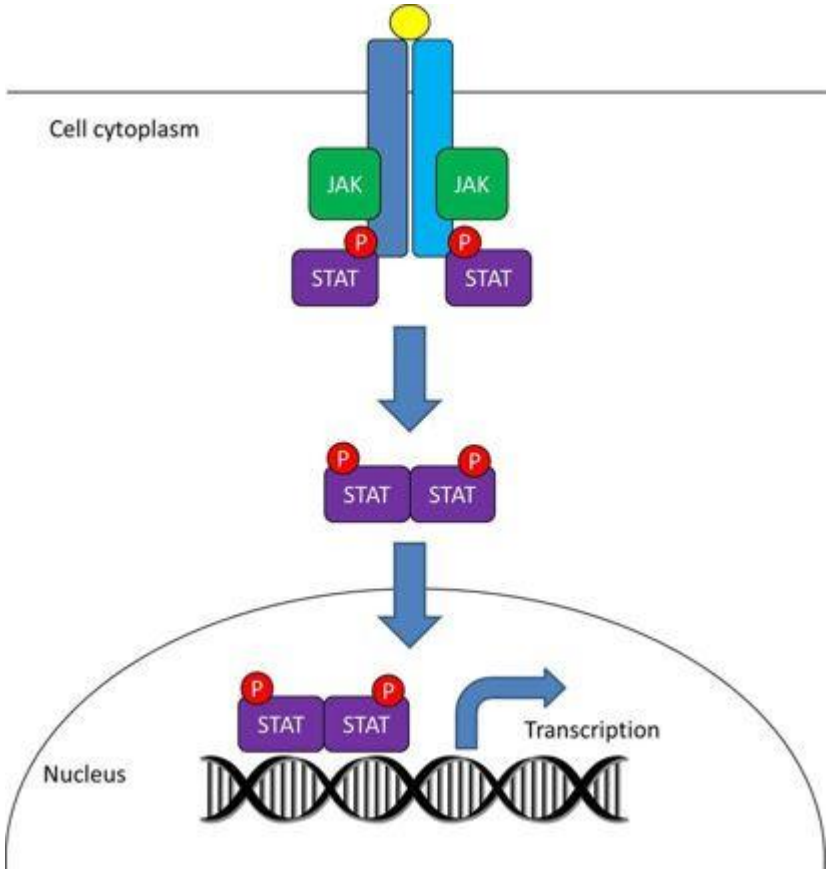
Clinical responses to biologics vs. methotrexate



DOI: 10.5772/53321

Small molecule inhibitors

- Jak inhibitors (downstream of cytokine receptor signaling)
  - Tofacitinib
  - Baricitinib
  - Upadacitinib



Glucocorticoids

- Potent anti-inflammatory drugs
- Serious adverse effects with long-term use
- To control the disease
- Indications
  - As a bridge to effective DMARD therapy
  - Systemic complications (e.g. vasculitis)
- Increases risk of infection by 67%

Prednisone

- Sodium retention, Fluid retention , Congestive heart failure in susceptible patients, Potassium loss, Hypokalemic alkalosis, Hypertension
- Muscle weakness, Steroid myopathy, Loss of muscle mass, Osteoporosis, Tendon rupture, particularly of the Achilles tendon, Vertebral compression fractures, Aseptic necrosis of femoral and humeral heads, Pathologic fracture of long bones
- Peptic ulcer with possible perforation and hemorrhage, Pancreatitis, Abdominal distention, Ulcerative esophagitis, Increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.
- Impaired wound healing, Thin fragile skin, Petechiae and ecchymoses, Facial erythema, Increased sweating, May suppress reactions to skin tests
- Negative nitrogen balance due to protein catabolism
- Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment, Convulsions, Vertigo, Headache
- Menstrual irregularities, Development of Cushingoid state, Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness Suppression of growth in children, Decreased carbohydrate tolerance, Manifestations of latent diabetes mellitus, Increased requirements for insulin or oral hypoglycemic agents in diabetics
- Posterior subcapsular cataracts, Increased intraocular pressure, Glaucoma, Exophthalmos
- Atypical and typical infections

Oral disease modifying therapies in SLE

- Hydroxychloroquine * ϕ
- Azathioprine
- Mycophenolate
- Methotrexate
- Leflunomide
- Cyclophosphamide
- Dapsone
- Glucocorticoids ϕ

*Quality metric ϕ FDA Approved

Biologics in SLE

- Belimumab*
- Rituximab
- Abatacept
- Anifrolumab – pending FDA review
- Tocilizumab

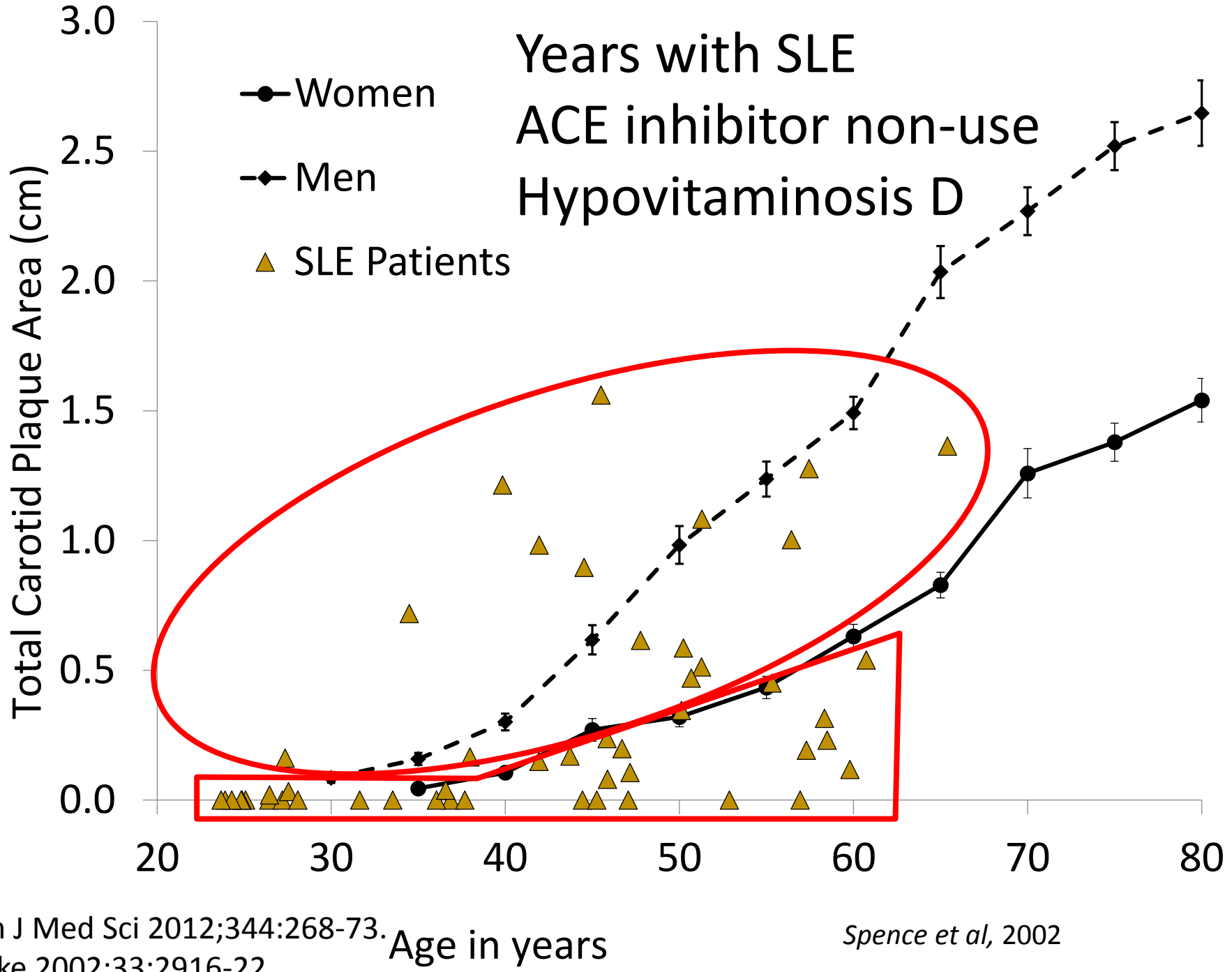
*FDA approved

Cardiovascular disease in SLE

TABLE 4. Comparison of risk factors between women who had systemic lupus erythematosus with and without cardiovascular events, University of Pittsburgh, 1980–1993

Risk factors	Cardiovascular event* (*n* = 33)		No event (*n* = 465)		*p* value†	RR‡	95% CI‡
	No	%	No.	%			
Non-Caucasian	6	18	93	20	0.97	0.57	0.23–1.42
Renal disease	10	30	101	21	0.35	1.51	0.69–3.32
Pericarditis	6	18	51	11	0.33	0.92	0.37–2.25
Hypertension	24	72	295	63	0.37	1.16	0.52–2.57
Hypercholesterolemia	6	18	21	4	0.003	3.35	1.34–8.36
Diabetes	4	12	27	5	0.28	1.98	0.69–5.71
Family history of cardiovascular disease	12	36	150	32	0.76	1.64	0.79–3.39
Postmenopause	16	48	138	29	0.03	0.77	0.24–2.46
Corticosteroid use	29	87	383	82	0.56	0.57	0.19–1.67
Duration of use§					0.002	0.98	0.94–1.03
Maximum dose¶					0.59	1.00	0.99–1.01
Tobacco							
Use	19	57	248	53	0.77	1.33	0.66–2.70
Pack-years#					0.33	1.01	0.99–1.03

	Cardiovascular event (mean years)	No event (mean years)	*p* value	RR	95% CI
Age at lupus diagnosis	39	34	0.02	1.21	1.09–1.35
Lupus disease duration	13	10	0.01	0.83	0.74–0.92



Ravenell RL, et al. Am J Med Sci 2012;344:268-73.
Spence JD, et al. Stroke 2002;33:2916-22.

Spence et al, 2002

Predictors of CVD in SLE

- Age
- Sex
- SBP
- Total cholesterol
- HDL
- SLEDAI (mean over time)
- Low C3
- Lupus anticoagulant
- If all of the above, 10 year risk = 45%

Lupus Sci Med. 2019 Oct 10;6(1):e000346.

Medication and risk for CVD in SLE

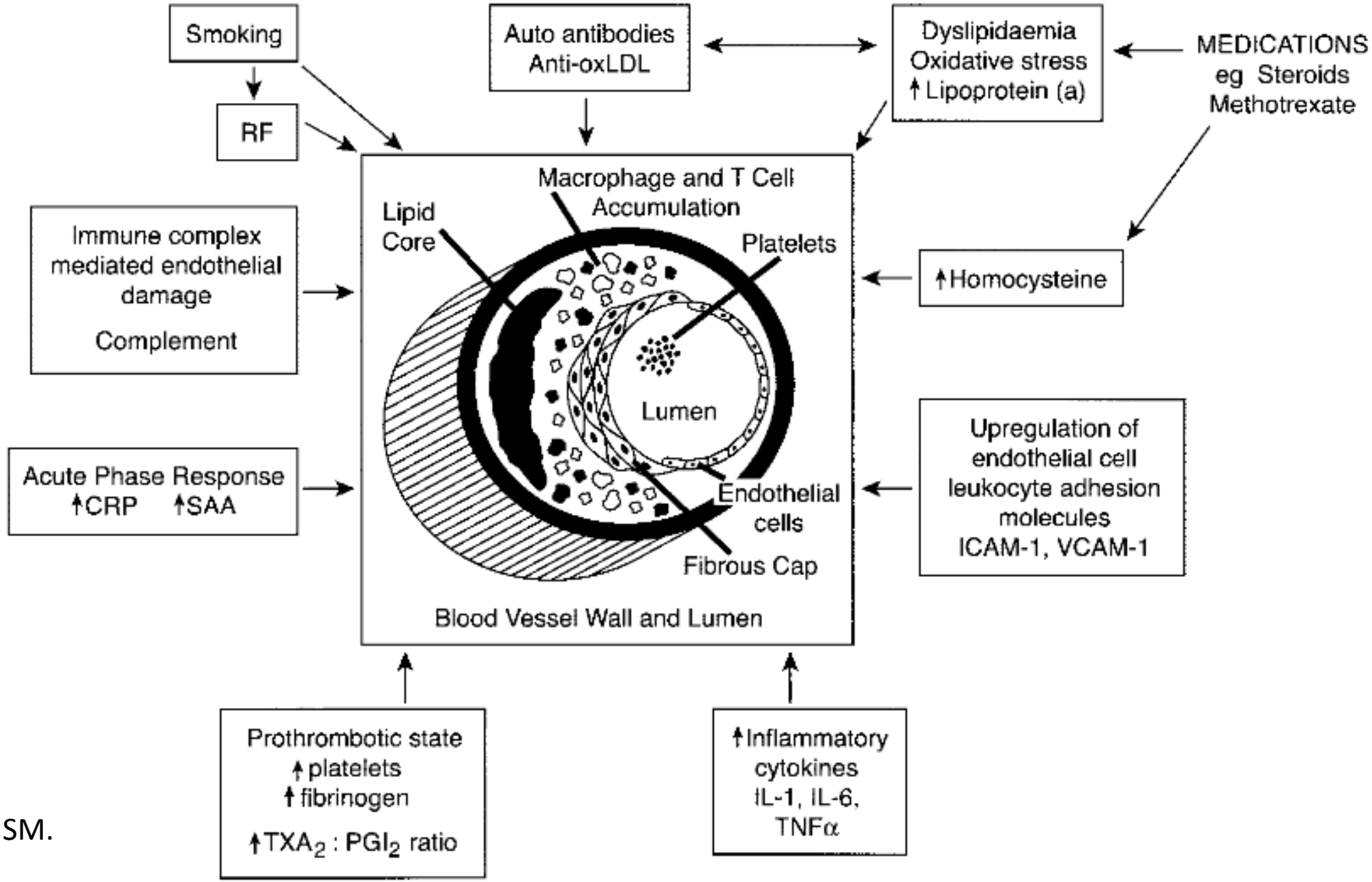
- Dose and duration of prednisone use
  - Mean daily prednisone ≥ 7.5 mg = higher risk of CVD (HR 1.54)
  - Mean daily prednisone ≥ 7.5 mg = higher risk osteoporotic fracture (2.41)
- Hydroxychloroquine protective

Lupus Sci Med. 2015; 2(1): e000066.
Circulation. 2005;112:3337–3347

Vascular disease in RA

- 50% of CVD in RA not accounted for by Framingham risk factors
- CRP predictive of future events
- Standardized mortality ratio 0.9 to 3.0 in RA with 34-40% due to CVD

ARTHRITIS & RHEUMATISM. 2002, 46(4):862–873



ARTHRITIS & RHEUMATISM.
2002, 46(4):862–873

Predictors of Mortality in RA

- Health Assessment Questionnaire
  - 1 standard deviation – OR 2.31 (50% of model)
  - severely impaired functional status has been compared 3-vessel coronary artery disease or stage 4 Hodgkin's disease
- Global disease severity
  - 1 standard deviation – OR 1.83 (30% of model)
- 50% increase in death due to CVD in RA
  - Traditional risks increased by over 50%
- Presence of rheumatoid factor

Best Pract Res Clin Rheumatol 2007;21:871–83
Arthritis Rheum. 2003 Jun;48(6):1530-42.
Arthritis Rheum. 2008 Dec 15;59(12):1690-7.

HAQ

Multi-Dimensional Health Assessment Questionnaire (R808-NP2)

This questionnaire includes information not available from blood tests, X-rays, or any source other than you. Please try to answer each question, even if you do not think it is related to you at this time. Try to complete as much as you can yourself, but if you need help, please ask. <u>There are no right or wrong answers.</u> Please answer exactly as you think or feel. Thank you.

1. Please check (√) the ONE best answer for your abilities at this time:

OVER THE LAST WEEK, were you able to:	Without **ANY** <u>Difficulty</u>	With **SOME** <u>Difficulty</u>	With **MUCH** <u>Difficulty</u>	**UNABLE** <u>To Do</u>
a. Dress yourself, including tying shoelaces and doing buttons?	0	1	2	3
b. Get in and out of bed?	0	1	2	3
c. Lift a full cup or glass to your mouth?	0	1	2	3
d. Walk outdoors on flat ground?	0	1	2	3
e. Wash and dry your entire body?	0	1	2	3
f. Bend down to pick up clothing from the floor?	0	1	2	3
g. Turn regular faucets on and off?	0	1	2	3
h. Get in and out of a car, bus, train, or airplane?	0	1	2	3
i. Walk two miles or three kilometers, if you wish?	0	1	2	3
j. Participate in recreational activities and sports as you would like, if you wish?	0	1	2	3
k. Get a good night's sleep?	0	1.1	2.2	3.3
l. Deal with feelings of anxiety or being nervous?	0	1.1	2.2	3.3
m. Deal with feelings of depression or feeling blue?	0	1.1	2.2	3.3

FOR OFFICE USE ONLY

1.a-j **FN** (0-10): ☐

1=0.3	16=5.3
2=0.7	17=5.7
3=1.0	18=6.0
4=1.3	19=6.3
5=1.7	20=6.7
6=2.0	21=7.0
7=2.3	22=7.3
8=2.7	23=7.7
9=3.0	24=8.0
10=3.3	25=8.3
11=3.7	26=8.7
12=4.0	27=9.0
13=4.3	28=9.3
14=4.7	29=9.7
15=5.0	30=10

2.PN (0-10): ☐

4. Considering all the ways in which illness and health conditions may affect you at this time, please indicate below how you are doing:

VERY WELL ○ VERY POORLY

0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10

CVD and our therapies

- Lower mortality on TNFα inhibitors IF patients respond to therapy at 6 months
- Risk of MI accounted for by traditional risk factors plus
  - Use of corticosteroids

Arthritis Rheum. 2007 Sep;56(9):2905-12.
Arthritis Rheum. 2008 Sep;58(9):2612-21

Therapy and mortality in RA

- Methotrexate associated with 60% reduction in mortality
- Methotrexate non-responders had 5.6-fold increase in mortality over the general population

Arthritis Rheum 2000;**43**:14–21.
Lancet 2002;**359**:1173–7

RA mortality aside from CVD

- Infection, particularly pneumonia
- COPD, pulmonary fibrosis
- Non-Hodgkin’s lymphoma
- Lung cancer (linked to smoking)

Best Pract Res Clin Rheumatol 2007;21:871–83

Demographic predictors of mortality in RA

- Age
- Male gender

Predictors of mortality in SLE

- Age > 50 at diagnosis (HR 5.9)
- Male gender (RH 2.4)
- Annual family income < $25k
- Low complement during the first year

- Bimodal distribution of mortality in SLE
  - Active disease and infection early
  - Cardiovascular disease late

Medicine (Baltimore). 2006 May;85(3):147-56.

Bottom line

- Effective therapy reduces mortality and CVD
  - Supports “treat-to-target” approaches
- Glucocorticoids increase mortality
- Traditional and disease-related factors contribute to CVD in RA and SLE
  - Supports “treat to target” approach
  - Supports aggressive management of traditional risk factors

Objectives

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- Serologies in autoimmune disease
- Newer biologics for connective tissue diseases
- Connective tissue disease as risk factor for atherosclerotic disease
- Predictors of mortality in CTD