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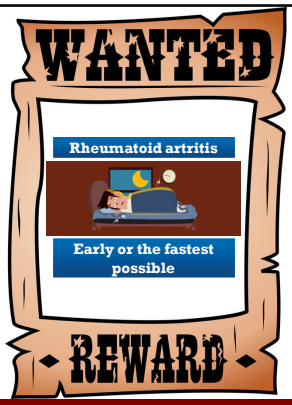
Rheumatoid artritis

Dr. Klaas Vandevyvere



- Changing diagnostic and therapeutic landscape for rheumatoid arthritis
- Klaas Vandevyvere MD, AZ West

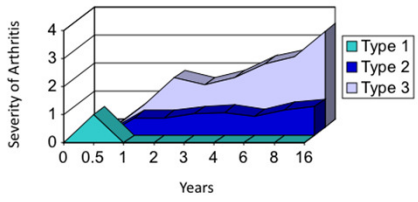
Overview

- What is the pathogenesis of RA?
- How do you diagnose RA?
- What clinical manifestations must one be aware of?
- Is there a window of opportunity to make a difference?
- Current treatment principles:
  - Medications used
  - Treat to target
  - When to introduce newer agents
- Complications of therapy

Introduction

- Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint inflammation and destruction in association with serological evidence of autoreactivity.
- Affects approximately 1% of the population and causes significant morbidity and mortality, with accelerated atherosclerosis impairing life expectancy.
- In the past two decades, the therapy of RA has undergone revolutionary change, reflecting a paradigm shift in treatment approach as well as the introduction of new disease-modifying antirheumatic drugs (DMARDs), most prominently the biological agents, including the tumor-necrosis-factor (TNF) blockers.

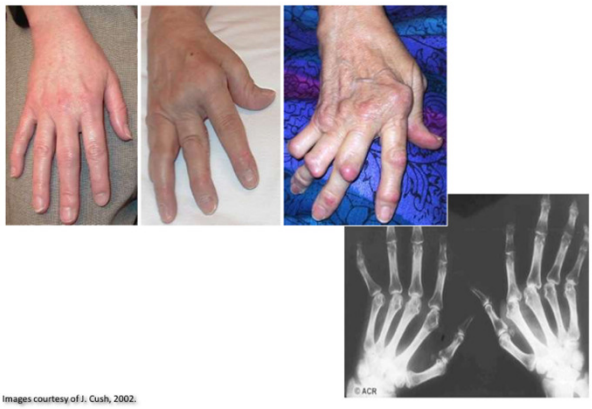
Clinical Course of RA



Type 1 = Self-limited—5% to 20%
Type 2 = Minimally progressive—5% to 20%
Type 3 = Progressive—60% to 90%

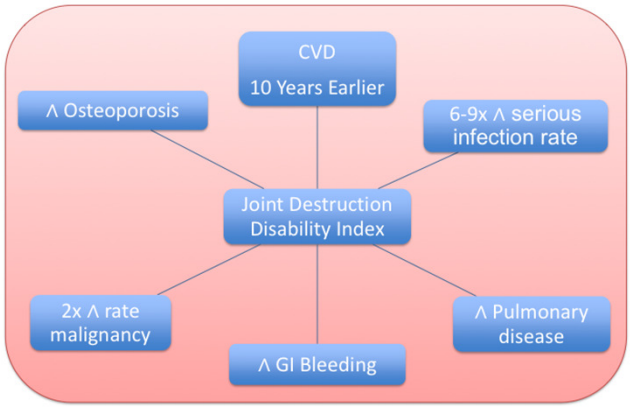
Pincus. *Rheum Dis Clin North Am.* 1995;21:619.

Clinical Spectrum of RA



Images courtesy of J. Cush, 2002.

RA: It's not just the joints



Poor prognostic factors

- Extra-articular signs and symptoms (e.g. Cutaneous ulcers, vasculitic rash, neuropathy, scleritis, subcutaneous nodules)
- Female gender
- Shared epitopes
- Poor functional status
- Involvement of multiple joints
- Early radiographic evidence of erosive changes
- Advanced age at onset of disease
- High RF titer
- Sustained elevation of acute-phase reactants (e.g. ESR)
- Low socioeconomic status/educational level
- High titre CCP antibody
- Smoking

Anaya JM, et al. Ann Rheum Dis. 1994;53:782–783; Pincus T, Callahan LF. Balliere's Clin Rheumatol. 1992;6:161–191; Furst DE. Rheum Dis Clin North Am. 1994;20:309–319.

Diagnosing RA

1987 Revised ACR Classification of RA

Criterion	Definition
Morning stiffness	Lasting ≥ 1 hour before maximal improvement
Arthritis ≥ 3 joints	Clinical evidence of soft tissue swelling or fluid in right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
Arthritis of hand joints	1 or more swollen areas in wrist, MCP, or PIP joint
Symmetric arthritis	Simultaneous involvement of same joint areas on both sides of body (bilateral involvement of PIP, MCP, or MTP joints is acceptable without absolute symmetry)
Rheumatoid nodules	Clinical evidence of subcutaneous nodules over bony prominences, extensor surfaces, or in juxtaarticular regions
Serum RF	Elevated rheumatoid factor measured by any method in which positive results are found in < 5% of normal subjects
Radiographic changes	Erosions or unequivocal body decalcification localized in or adjacent to involved joints on posteroanterior hand and wrist radiographs

Classification of RA is fulfilled when 4 of 7 criteria are present (first 4 criteria must be present for at least 6 weeks); another clinical diagnosis does not exclude RA.

2010 ACR/EULAR classification criteria for RA

A score of ≥6/10 is needed to classify RA

	Score
A. Joint involvement	
❖1 large joint	0
❖2-10 large joints	1
❖1-3 small joints (with or without involvement of large joints)	2
❖4-10 small joints (with or without involvement of large joints)	3
❖>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed)	
❖Negative RF and negative ACPA	0
❖Low-positive RF or low-positive ACPA	2
❖High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed)	
❖Normal CRP and normal ESR	0
❖Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
❖<6 weeks	0
❖≥6 weeks	1

Aletaha et al. *Arthritis Rheum.* 2010;62:2569-2581
Aletaha et al. *Ann Rheum Dis.* 2010; 69:1580-1588

Antibodies to cyclic citrullinated peptides (anti-CCP)

- Anti-CCP has high diagnostic specificity for RA (98%)
- Found in 40% of patients who are RF negative
- Citrullination is the post-translational modification of arginine to citrulline
  - Alters the structure, antigenicity, and function of proteins
- Four candidate citrulllinated antigens have been established: fibrinogen, vimentin, type II collagen, α-enolase

Wegener et al. *Immunological Rev.* 2010;233:34

Rheumatoid factor (RF)

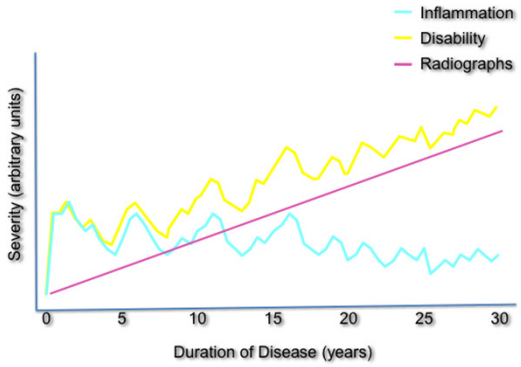
- Antibody reactive against Fc fragment of IgG
- 80% of RA patients are ever seropositive for RF, <50% in early RA, and is associated with:
  - More radiological abnormalities
  - More disease activity
  - Worse functional ability
  - More extra-articular manifestations
  - More treatment with second line drugs
- Not specific for RA: chronic infections, cirrhosis, malignancies, other rheumatic diseases.

Is there a window of opportunity?

Window of opportunity

- Several studies have shown greater improvements with earlier treatment.
- Can that concept be taken to an extreme, so that these agents be started at the earliest point in diagnosis?
- This has been codified as the "Window of opportunity hypothesis," which posits that, early in its course, RA displays a unique phenotype in which immunoregulatory disturbances can be decisively or permanently blocked

RA Progression

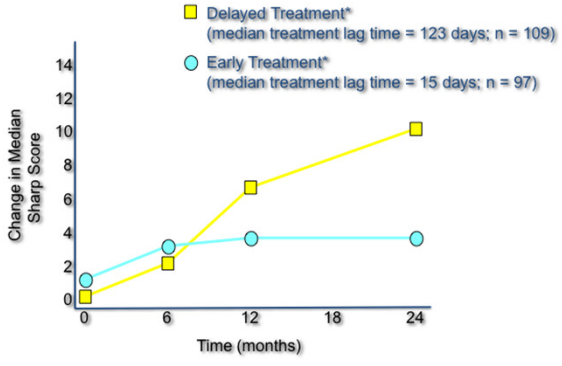


Adapted from Kirwan JR. *J Rheumatol.* 2001;28:881–886.

Principles of Therapy

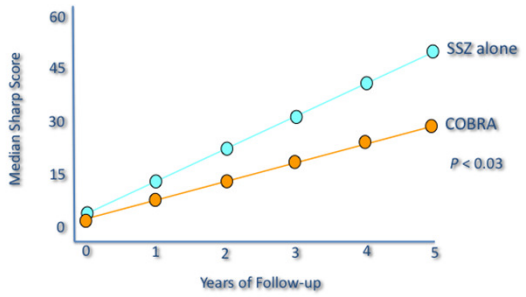
- EARLY initiation of therapy
- Treat to target
- Combine medications to achieve remission

Treatment: The Earlier the Better



*Patients were treated with chloroquine or azathioprine.
Lard LR, et al. *Am J Med.* 2001;111:446–451.

COBRA Trial
Early Intervention Yields Long-Term Benefits



COBRA: Prednisolone (initially 60 mg/d, tapered in 6 weekly steps to 7.5 mg/d) + methotrexate 7.5 mg/wk x 40 wks + sulfasalazine 2 g/d.
SSZ: Sulfasalazine 2 g/d.

Landewé RBM, et al. Arthritis Rheum. 2002;46:347-356.

Quantitative Measures of Disease Activity

Patient Only
- Patient activity scale (PAS) or PASII
- Routine assessment of patient index data 3 (RAPID 3)

Patient and provider data
- Clinical disease activity index (CDAI)

Patient, provider, and lab data
- Disease activity score with the 28-joint count (DAS28)
- Simplified disease activity index (SDAI)

Features of Disease Activity Measurement Tools

DAS28
- Requires assessment of 28-joint count and either ESR or CRP level
- Involves difficult calculation

CDAI
- Requires assessment of 28-joint count, physician global assessment, and patient global assessment
- Does not require a laboratory test

SDAI
- Requires assessment of 28-joint count, physician global assessment, and patient global assessment, plus ESR

RAPID 3
- Requires 3 measures of physical function, pain, and patient global assessment of status
- All 3 components reported by the patient
- Involves simple addition of 3 measures

Assessing Disease Activity in RA

	Level of Disease Activity			
Instrument	**Remission**	**Low**	**Moderate**	**High**
DAS28 (range, 0-9.4)	< 2.6	≥ 2.6 to < 3.2	≥ 3.2 to ≥ 5.1	≥ 5.1
PAS or PAS-II (range, 0-10)	0 to 0.25	0.26 to 3.7	3.71 to < 8.0	≥ 8.0
CDAI (range, 0-76)	≤ 2.8	> 2.8 to 10.0	> 10.0 to 22.0	> 22.0
RAPID 3 (range, 0-30)	0 to 3.0	> 3.0 to 6.0	> 6.0 to 12.0	> 12.0 to 30.0
SDAI (range, 0-86)	≤ 3.3	> 3.3 to ≤ 11.0	> 11.0 to ≤ 26.0	> 26.0

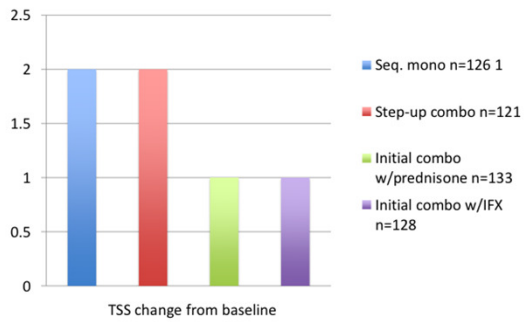
BeSt: Treatment Strategies

Group 1 Monotherapy	Group 2 Step-Up Therapy	Group 3 Combo Therapy	Group 4 MTX + INF
MTX	MTX	MTX + SSZ + PRED	MTX + INF
SSZ	MTX + SSZ	MTX + CsA + PRED	SSZ
LEF	MTX + SSZ + HCQ	MTX + INF	LEF
MTX + INF	MTX + SSZ + HCQ + PRED		MTX + CsA + PRED
	MTX + INF		

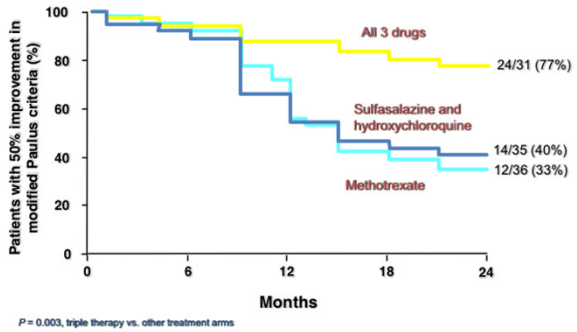
Legend:
CsA = cyclosporin A; **HCQ** = hydroxychloroquine; **INF** = infliximab; **LEF** = leflunomide; **MTX** = methotrexate; **PRED** = prednisone; **SSZ** = sulfasalazine

BeST Study

Treatment Strategies in Early Rheumatoid Arthritis: Clinical and Radiological Outcomes After 2-year Follow-Up

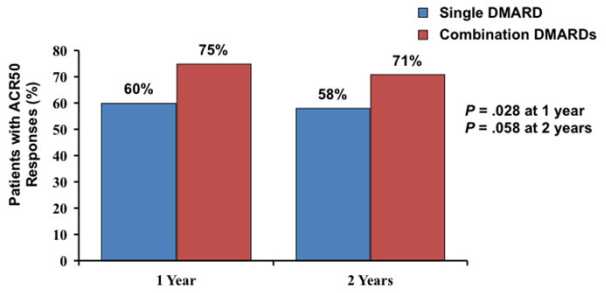


Triple Therapy:
Proportion of Patients with Sustained Response



P = 0.003, triple therapy vs. other treatment arms

Combination Methotrexate, Sulfasalazine, and Hydroxychloroquine (FIN-RACo Study)



199 patients with early RA were randomly assigned to combination therapy with methotrexate 7.5 mg/week, sulfasalazine 1 g/day, hydroxychloroquine 300 mg/day, and prednisolone 5 mg/day (with flexible dosage adjustment to achieve remission), or single DMARD therapy with sulfasalazine 2 g/day with or without prednisolone. If necessary because of adverse events or lack of efficacy, sulfasalazine was replaced by methotrexate and subsequently azathioprine

Mottonen T et al. *Lancet*. 1999;353:1568-1573.

What to treat with

RA: Current Pharmacologic Options

- Agents that are effective in controlling the signs and symptoms of RA, but have no effect on disease progression
  - NSAIDs reduce inflammation and pain
  - COX-2 inhibitors are similar to NSAIDs, but with improved GI safety and tolerability and higher cardiac side effects
  - Analgesics- these medicines do not affect inflammation, but work on pain pathways to decrease subjective feeling of pain.
- DMARDs impact the signs, symptoms, and disease progression of RA, as well as improve the quality of life and functionality of the patient
- Corticosteroids have anti-inflammatory and immunoregulatory activity, but nominal disease-modifying capability

Irvine S, et al. *Ann Rheum Dis*. 1999;58:510–513; Madhok R, Capell HA. *Lancet* 1999;353:257–258; ACR Subcommittee on RA Guidelines. *Arthritis Rheum*. 2002;46:328–346; Goldbach-Mansky R, Lipsky PE. *Annu Rev Med*. 2003;54:197–216.

RA: Disease Modifying therapies

Traditional DMARDs

For example

- Methotrexate
- Leflunomide (Arava®)
- Sulfasalazine (SSZ, Azulfidine®)
- Hydroxychloroquine (HCQ, Plaquenil®)
- Azathioprine, cyc losporine

Biological DMARDS

For example

- TNF antagonists
  - Etanercept (Enbrel®)
  - Adalimumab (Humira®)
  - Infliximab (Remicade®)
  - Certolisumab pegol (Cimzia®)
  - Golimumab (Simponi®)
- Abatacept (Orencia®)
- Rituximab (Rituxan®)
- Tocilizumab (Actemra®)
  - * **Sarulimab (Kevzara)**
- Tofacitinib (Xeljanz®)
  - * **Baricitinib (Olumiant)**

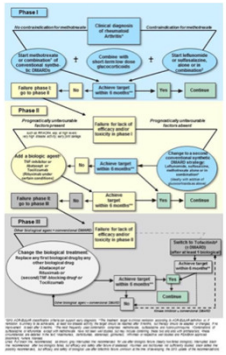
Methotrexate

- Most effective single DMARD (used as baseline therapy in most patients.) Typical dose is 15 mg/week.
- Good benefit-to-risk ratio.
- Screen Hepatitis serologies before use, ETOH counseling, LFT, CBC, creatinine prior to use and every 2-3 months.
- Side effects include liver damage, oral and mucosal ulcers and rarely lung toxicity. Rarely may cause bone marrow suppression.
- Must be taken with folic acid supplementation. 1mg every day except on day of MTX.
- Avoid use with TMP/SMX: bone marrow suppression.

TNF antagonists

- 5 currently approved agents:
  - Etanercept, adalimumab, infliximab, certolizumab pegol, golimumab.
- Subcutaneous (etanercept, adalimumab, certolizumab pegol, golimumab) and intravenous administration (infliximab and golimumab.)
- Administration in combination with MTX is superior to monotherapy.
- Time to onset: rapid (weeks)
- Adverse events:
  - Infection, TB, multiple sclerosis/demyelination, lupus-like syndrome.
  - Malignancy: higher rates as compared with normal population but not higher than the background of lymphoma and solid tumors in RA population. Increased risk of non melanotic skin cancers.
- Monitoring:
  - TB screening including PPD prior to therapy.
  - Periodic CBC, LFTs.
  - Infection.

Algorithm based on the 2013 European League Against Rheumatism recommendations on rheumatoid arthritis management.



Josef S Smolen et al. Ann Rheum Dis
doi:10.1136/annrheumdis-2013-204573

ARD

Special situations: Urgent issues

- Fever and infections
- Septic arthritis
- Dyspnea and cough in a patient on MTX
- Pre-op issues in long standing RA

Infections in RA

- Infections in RA increased (up to 6 to 9 fold)
  - Immune dysfunction of RA.
  - Corticosteroids, even "low dose."
  - Immunomodulatory drugs, in particular biologic therapies.
- Assessing RA patient with fever, suspected infection
  - Prompt and thorough evaluation of symptoms
  - Prompt initiation of antibiotics (especially for patients on biologics)
    - Avoid use of trimethoprim/sulfamethoxazole (Bactrim®, Septra®) in patients on MTX
- Usual bacterial culprits, skin and soft tissue infections, as well as rare infections
- Opportunistic organisms (especially with biologics)
  - Mycobacterial (atypical or disseminated presentation)
  - Fungal (eg. *Histoplasma, Coccidioides, Cryptococcus, Aspergillus, Candida*)
  - Viral (e.g. Zoster)

Table 5. 2012 American College of Rheumatology recommendations update regarding the use of vaccines in patients with RA starting or currently receiving DMARDs or biologic agents*

	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumococcal†	Influenza (intramuscular)	Hepatitis B‡	Human papillomavirus	Herpes zoster
Before initiating therapy					
DMARD monotherapy	√	√	√	√	√
Combination DMARDs§	√	√	√	√	√
Anti-TNF biologics¶	√	√	√	√	√
Non-TNF biologics#	√	√	√	√	√
While already taking therapy					
DMARD monotherapy	√	√	√	√	√
Combination DMARDs	√	√	√	√	√
Anti-TNF biologics¶	√	√	√	√	Not recommended**
Non-TNF biologics#	√	√	√	√	Not recommended**

* Evidence level was C for all of the vaccination recommendations. For definitions and key terms, please refer to Table 2. DMARDs = disease-modifying antirheumatic drugs; √ = recommend vaccination when indicated (based on age and risk); anti-TNF = anti–tumor necrosis factor.
† The Centers for Disease Control and Prevention also recommends a one-time pneumococcal revaccination after 5 years for persons with chronic conditions such as rheumatoid arthritis (RA). For persons ages ≥65 years, one-time revaccination is recommended if they were vaccinated ≥5 years previously and were age <65 years at the time of the primary vaccination.
‡ If hepatitis risk factors are present (e.g., intravenous drug abuse, multiple sex partners in the previous 6 months, health care personnel).
§ DMARDs include hydroxychloroquine, leflunomide, methotrexate, minocycline, and sulfasalazine (listed alphabetically) and combination DMARD therapy included double (most methotrexate based, with few exceptions) or triple therapy (hydroxychloroquine + methotrexate + sulfasalazine).
¶ Anti-TNF biologics include adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab (listed alphabetically).
# Non-TNF biologics include abatacept, rituximab, and tocilizumab (listed alphabetically).
** According to the RAND/UCLA Appropriateness Method, panel members judged it as "not appropriate" and therefore it qualifies as "not recommended" (median score on appropriateness scale was 1).

Conclusions

- Early introduction of effective treatment with minimal delay in introduction of combination therapy, including prednisolone or TNF blockers
- Result-driven (for instance DAS ← 2.4 or remission) treatment
- Tight-controlled (based on measurement of disease activity) treatment
- New trials will help tot fine tune the timing of the most effective drugs, which include the newer biologicals.

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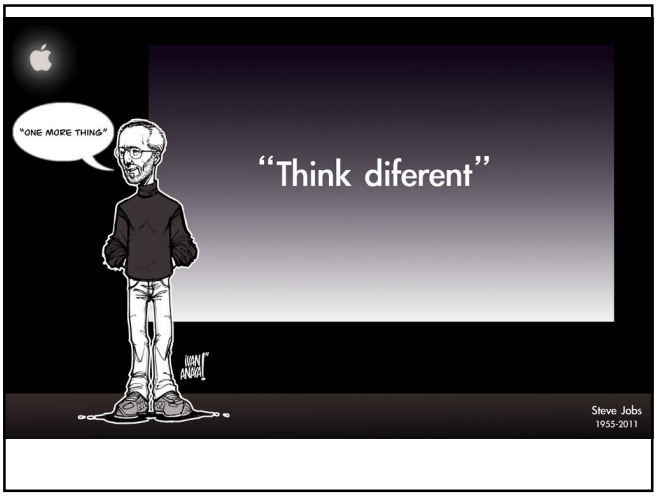

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