

A Snapshot of Inflammatory Arthritis

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Rheumatologist

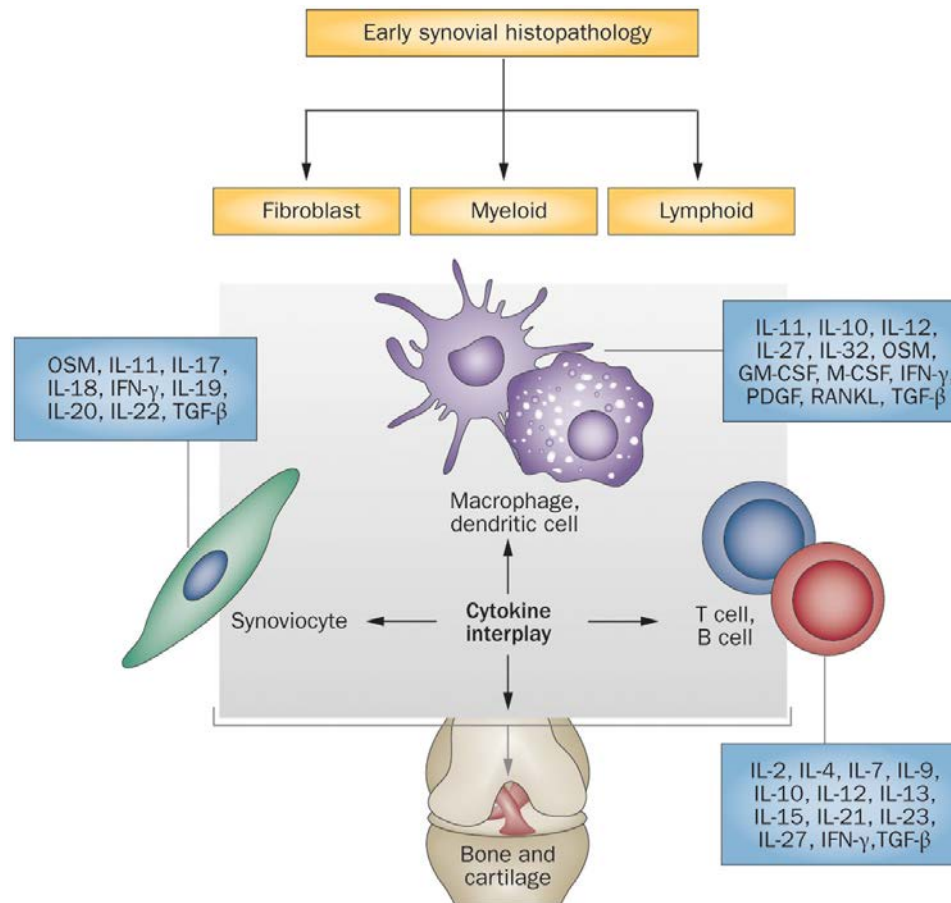
Physician VMO Calvary hospital

1st April 2016

Def: inflammatory arthritis

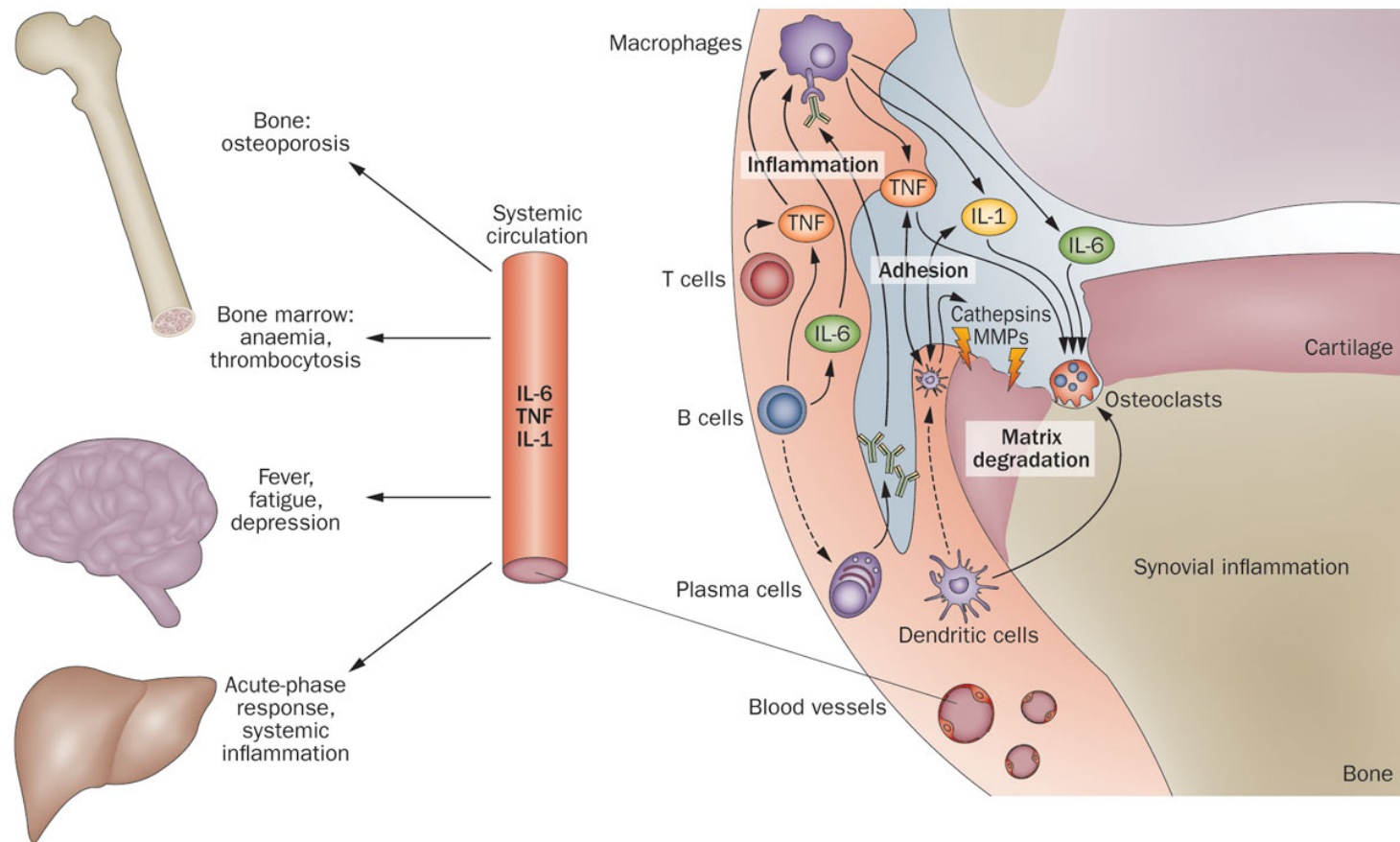
- **History** : EMS, improve activity, night awakening, response to NSAIDs
- **Clinical** : red, hot , swollen and pain ,reduce mobility/function
- **Pathology**: influx of inflammatory cells into synovial membrane/fluid causing hyperplasia of synovial fibroblast
 - lead to damage cartilage and bone – its destruction

Figure 2 Cytokine network in RA: overlap and interplay between cytokines drives synovial inflammation



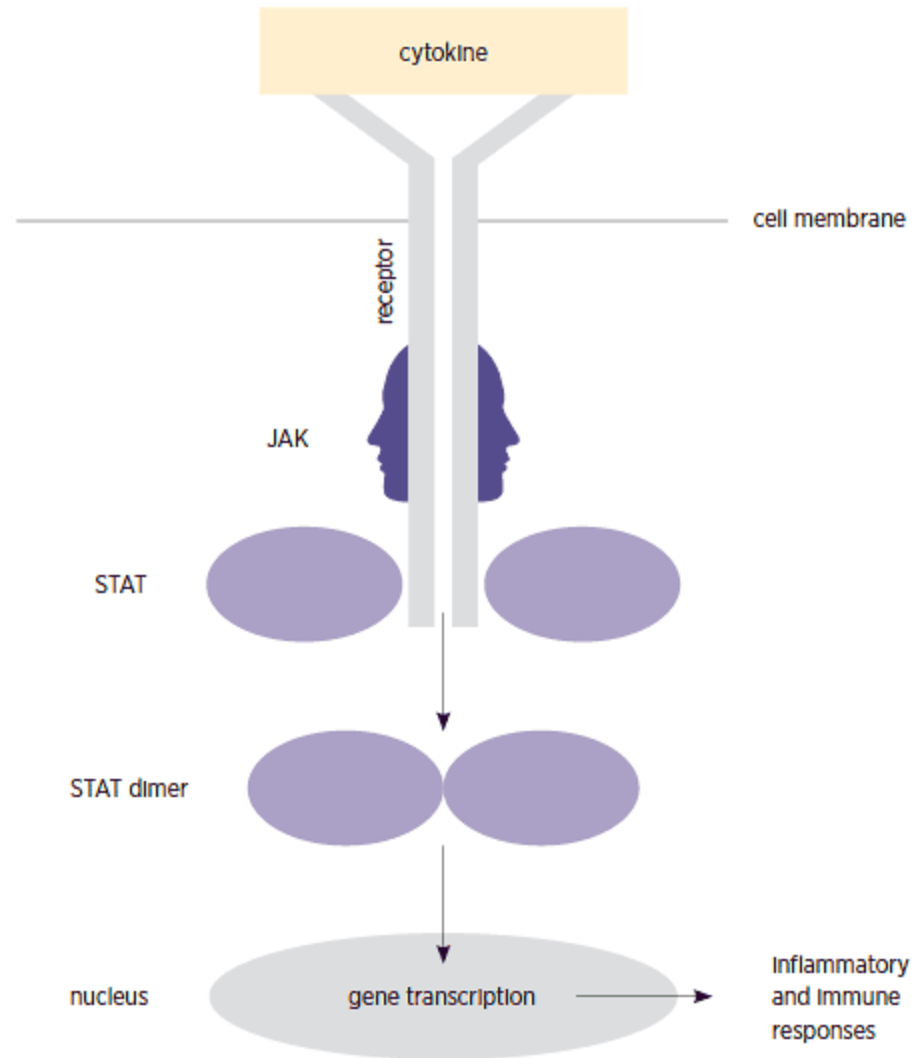
Choy, E. H. *et al.* (2013) The problem of choice: current biologic agents and future prospects in RA
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2013.8

Figure 1 Pathogenesis of RA: synovial and systemic inflammation



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Fig. Signalling through the JAK-STAT pathway



JAK Janus kinase STAT Signal Transducer and Activation of Transcription



Differential for Inflammatory arthritis

- RA- seronegative/seropositive
- Axial and peripheral spondyloarthritis (SpA) -
 - PSA
 - Ank spond
 - Reactive
 - Enteropathic
 - Undifferentiated
 - Juvenile
- Crystal arthritis
- AI ds – SLE , SSc, MCTD, AOSD etc
- Others – virals, vasculitides, septic arthritis, paraneoplastic

Differential Inflammatory arthritis (2)

- **Undifferentiated early inflammatory arthritis (UIA)**
 - Diagnosis by exclusion made in patients with arthritis not sufficient to meet criteria of specific ds.
 - at least one clinically swollen joint is similar to the entry requirement for the use of the 2010 ACR/EULAR.
 - Arthralgia or findings such as pain on motion or tenderness upon pressure, are **not** sufficient
 - typically between 6/52 to a year in duration, although a diagnosis can often be determined within three months
 - Many such patients will eventually be diagnosed with rheumatoid arthritis (RA)

2010 ACR/EULAR Criteria for RA Diagnosis

A.	Joint involvement	
	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	>10 joints (≥ 1 small joint)	5
B.	Serology (≥ 1 test result 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 (≥ 1 test result needed)	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D.	Duration of symptoms	
	<6 wk	0
	≥ 6 wk	1
Definite diagnosis requires total score $\geq 6/10$.		

Epidemiology and natural history of UIA

- The annual incidence of inflammatory arthritis in studies of early arthritis cohorts ranges from 115 to 271 per 100,000 adults (The epidemiology of early inflammatory arthritis, Hazes et al. Nat Rev Rheum 2011)
 - 70 % specific diagnosis could be made at presentation (1/3 being RA)
 - incidence of undifferentiated arthritis (UA) ranged from 41 to 149 per 100,000 adults
 - Some dx as OA, SpA , spontaneous remission (40%) or remains UIA. (Ann Rheum Dis 2013;72:1436–1444)

Characteristic/clinical features of UIA

- Cohort of 776 patients prospectively evaluated in an early arthritis clinic in the Netherlands
- Symptoms of arthritis from several weeks to months. The median duration 13.4 weeks (5.3-29.2 weeks)
 - Morning stiffness
 - < 30 min (46%)
 - 30 to 59 min (16 %) , and
 - at least an hour (39 %)
 - Joint examination showed a swollen joint count
 - < less than four, (65%)
 - 4 to 10 (29%),
 - and greater than 10 (6%)
- ●Arthritis affected the upper extremities (76%), mostly hands , with symmetrical involvement (48%)
- ●Laboratory testing
 - Normal CRP and ESR (> 50%)
 - although some patients did have elevated levels (median ESR 16, median CRP 8).
- ●RF and/or ACPA +ve in 10%

Important features area:

- **History**
- current symptoms of arthritis, a past diagnosis of arthritis and features to look at differentials
 - infectious illness – genitorurinary tract, gastroenteritis
 - A recent viral syndrome, hepatitis, may suggest an infectious etiology
 - Symptoms of a spondyloarthritis (SpA), such as inflammatory back pain, enthesitis
 - Psoriasis,
 - Symptoms of IBD- abdominal pain, diarrhea, blood, or mucus in the stool
 - Uveitis or other eye disease - SpA, sarcoid, Behçet's syndrome etc.
 - Symptoms of systemic rheumatic disease - fever, Raynaud phenomenon, alopecia, cutaneous eruptions, mucosal ulcers, pleurisy, pericarditis, and neurologic symptoms
 - Symptoms of malignancy, including anorexia, unexplained weight loss, lymphadenopathy, or other changes
- The family history – any arthritis, particularly inflammatory arthritis; systemic rheumatic disease (eg, SLE); psoriasis: or inflammatory bowel disease.

Clinical examination

- A thorough physical examination.
- Signs of extra-articular disease
 - cutaneous disease, such as psoriasis, SLE, nodules
 - LN, glands
 - Detailed musculoskeletal exam to
 - confirm the presence of inflammatory arthritis,
 - characterize the involved joints, and
 - to identify signs of enthesitis or axial disease.

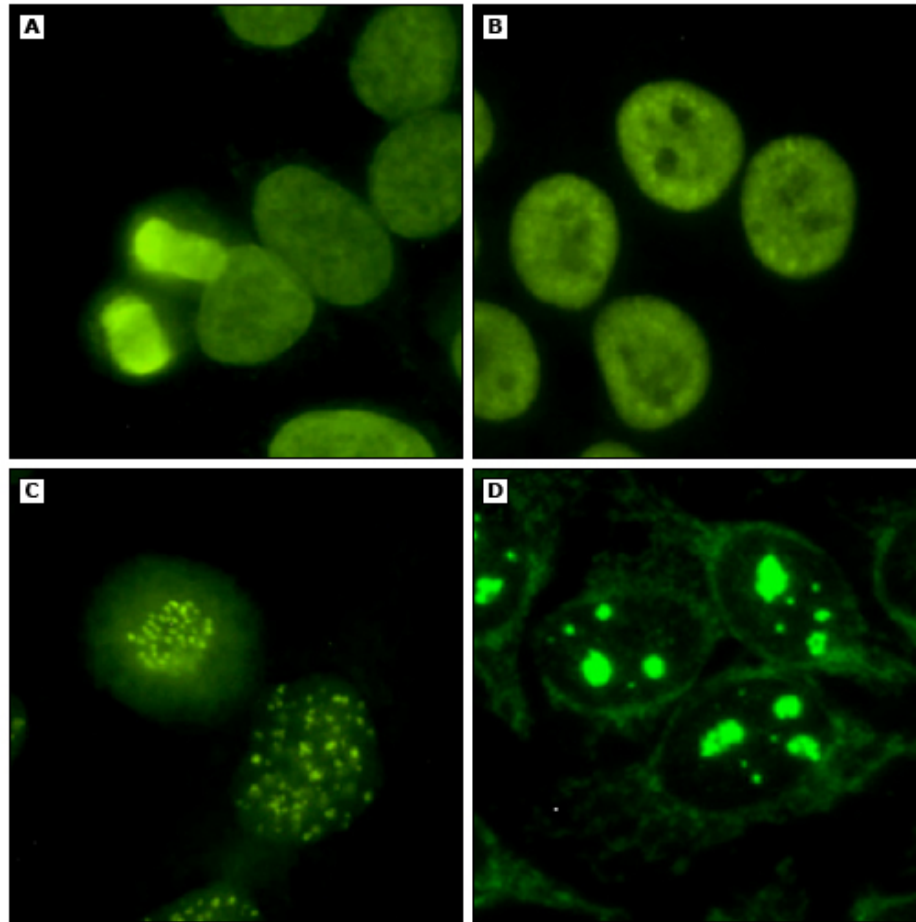
Laboratory testing – Laboratory testing should include:

- Baseline – FBC, EUC, LFT - aminotransferases, urate ,TSH , ESR, CRP
- •Autoantibody testing
 - RF and ACPA, ANA
- Hints
 - ANA is not specific, 5-8% normal population
 - ANA staining pattern are loosely associate with underlying AI disease.
 - ANA≠ SLE diagnosis, unlikely to have SLE if ANA -ve
 - ANA titre changes is not helpful in monitoring of disease activity
 - The higher the clinical probability of AI ds, the ANA are more likely to assist in establishing the diagnosis.

Disease Associated with positive ANA

Systemic AI Disease	% with positive ANA	Other causes	% with positive ANA
SLE	90-100	hashimoto	50
scleroderma	95	Graves	50
RA	45	AI hepatitis	70
Sjogren's syndrome	60	PBC	50-70
MCTD	100	Viral(EBV, HIV,HCV)	-
PM/DM	35	bacterial	-
Raynaud	40	malignancy	-
Drug induced LE	80-95%	IBD or ILD	-
		Source: Up to	date

Four common ANA staining patterns



In the homogeneous pattern (A), the entire nucleus is diffusely stained. The chromosomes at the metaphase plate are also stained. In the speckled pattern (B), very small, uniform, fluorescent dots are seen throughout the nucleus. The centromere pattern (C) is characterized by the presence of 30 to 60 dots distributed throughout the nucleus in resting cells. The dots localize to chromosomes at the metaphase plate in dividing cells. The nucleolar staining pattern is shown in (D).

Courtesy of Donald B Bloch, MD.

Rheumatoid antibody

- Sensitivity of RF (71%) and ACPA (66%) for RA is quite similar
- ACPA has greater specificity (90.4%), RF (80.3%)
 - (ACPA occur in about 5 to 15 percent of patients with PsA, Sjögren's syndrome, etc.)
- RF can be seen in other systemic rheumatic diseases and chronic infections, including hepatitis.
- RF occur in 70% patient with RA, ACPA 70-80%
- There is about 80 % overlap of the two autoantibody.
- 20-30% patient with SLE has RF
- Anti CCP is better predictor of prognosis than RF

EXTENDED REPORT

Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study

C Rakieh,¹ J L Nam,^{1,2} L Hunt,^{1,2} E M A Hensor,^{1,2} S Das,¹ L-A Bissell,^{1,2}
E Villeneuve,^{1,3} D McGonagle,^{1,2} R Hodgson,^{1,2} A Grainger,^{1,2} R J Wakefield,^{1,2}
P G Conaghan,^{1,2} P Emery^{1,2}

ABSTRACT

Objectives To monitor progression to inflammatory arthritis (IA) in individuals with non-specific musculoskeletal (MSK) symptoms and positive anticyclic citrullinated peptide (anti-CCP) antibodies. To develop a pragmatic model to predict development of IA in this patient group.

Methods In this prospective observational cohort, patients with new non-specific MSK symptoms and positive anti-CCP were recruited from regional primary care and secondary care referrals. Clinical, imaging and serological parameters were assessed at baseline. Cox regression analysis was performed to identify predictors of progression to IA and develop a risk score to stratify patients at presentation.

Findings 100 consecutive patients (73 women, mean age 51 years) were followed up for median 19.8 months (range 0.1–69.0); 50 developed IA after a median 7.9 months (range 0.1–52.4), 34 within 12 months. The majority (43/50) fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism criteria for rheumatoid arthritis. A model for progression to IA was devised using four variables: tenderness of hand or foot joints, early morning stiffness ≥ 30 min, high-positive autoantibodies, and positive ultrasonographic power Doppler signal. None of the five individuals at low risk (score 0) progressed to IA, compared with 31% of 29 at moderate risk (1–2) and 62% of 66 at high risk (≥ 3). Adding shared epitope increased the number at low risk (score 0–1; 0/11 progressed).

Conclusions In patients presenting with non-specific MSK symptoms and anti-CCP, the risk of progression to IA could be quantified using data available in clinical practice. The proposed risk score may be used to stratify patients for early therapeutic intervention.

Others autoantibody

- If ANA +ve, then additional autoantibody testing, esp if a systemic rheumatic disease has not been excluded clinically and there are other signs or symptoms of such a condition.
 - Depending upon the clinical findings,
 - ENA – anti-Smith and anti-ribonucleoprotein, anti-Ro/SSA and anti-La/SSB, anti-Jo1, and anti-topoisomerase-1 antibodies.
 - dsDNA
 - Thyroid antibody

Auto-antibody	% present in condition	specificity	Auto-antibody	% present in the condition	specificity
dsDNA	SLE 40-70%	75-99%	PM/ScI	SSc 5-10% Inf myositis	
Ro60	Sub cut lupus 75%		Ribosomal P	SLE- 10-20%	
	SS 60%		RNA polymerase	SSc 20%	high
	SLE 30%		U1RNP	MCTD 100%	
	PBC 30%			SLE 30-40%	
	PM 20%			RA/SS/SSc/PM	
La	SS 20%	high	U3RNP	SSc 5-10%	ILD/skin/PH T/mysotiis
Scl 70 (topoisomerase1)	SSc 20-40%		Anti centromere antibody	Limited Scl 30%	
Sm	SLE 10-50%	55-100%		PBC 15%	
	MCTD			SLE 4%	

Auto antibody association with the conditions

Auto antibody	% present in condition	specificity	Auto antibody	% present in condition	specificity
Ro52	SLE 40%		SRP	IM- 10%	
	SS 75%		AMA	PBC 20%	
	PM 35%		sMA	AIH 35%	
	SSc 20%			PBC 30%	
Aminoacyl-tRNA	DM/PM 25-35%				
Jo-1 (most common)	20-30% PM				
	PM/ILD 60-70%				

Other antibodies and assays

- HLAB27
 - testing in patients suspect of SpA (50%) , especially Ank spondylitis (95%).
- Infection –
 - if symptom less than 6 weeks
 - such as parvovirus B19, RRV etc
 - not routinely screen from viral infections as usually transient, I do routinely for hepatitis
- ANCA –symptoms vasculitis
- Others: depend on suspicion of disease

Arthrocentesis

- **Arthrocentesis**

- Arthrocentesis should be performed in affected swollen joints
 - (exclude infectious arthritis or crystal disease)
- Help to delineate inflammatory or not?
- Ask for m/c/s, cell count, Gram Stain, crystals

Measure	Normal	Noninflammatory	Inflammatory	Septic	Hemorrhagic
Volume, mL (knee)	<3.5	Often >3.5	Often >3.5	Often >3.5	Usually >3.5
Clarity	Transparent	Transparent	Translucent-opaque	Opaque	Bloody
Color	Clear	Yellow	Yellow opalescent to	Yellow to green	Red
Viscosity	High	High	Low	Variable	Variable
WBC, per mm ³	<200	200-2,000	2,000-100,000	15,000->100,000	200-2,000
PMNs, percent	<25	<25	=50	=75	50-75
Culture	Negative	Negative	Negative	Often positive	Negative
Total protein, g/dL	1-2	1-3	3-5	3-5	4-6
Glucose, mg/dL	Nearly equal to blood	Nearly equal to blood	>25, lower than blood	<25, much lower than blood	Nearly equal to blood

Imaging:

- XRAY- In all patients of affected joint(s)
 - As a baseline and look for erosions (help with dx)
 - Those with hands symptom/finding only, need both hands/feet xray.
 - ERA may exhibit erosion in the feet even in the absence of local signs and symptoms of the feet.
 - In UIA , erosion found in 10 % .
 - Studies of radiographic changes in UIA have also shown that the presence of 2 or > erosions has higher risk dx RA (53%) in the near future and persistent disease (68%). The feet erosion are equally predictive . (Thabet et al. The prognostic value of baseline erosion in UIA, Art res Ther 2009, 11:R155).

Ultrasound

- confirm the presence of synovitis where there is uncertainty regarding joint involvement.
- It can help with patient education regarding their disease and attitude and adherence to medication. (KK wong et al., Int journ Rheum disease 2014)

A diagnostic algorithm for persistence of very early inflammatory arthritis: the utility of power Doppler ultrasound when added to conventional assessment tools

J E Freeston, R J Wakefield, P G Conaghan, E M A Hensor, S P Stewart, P Emery

Power doppler uses **strength of a returned sound wave** from anything that is moving to give the position and brightness: better for low flow situation such as synovium

ABSTRACT

Objectives: The aim of this study was to assess the value of power Doppler ultrasound (PDUS) in combination with routine management in a cohort of patients with very early inflammatory arthritis (IA).

Methods: 50 patients with ≤ 12 weeks of inflammatory symptoms with or without signs had clinical, laboratory and imaging assessments. Diagnosis was recorded at 12 months. Assuming a 15% pre-test probability of IA, post-test probabilities for various assessments were calculated and used to develop a diagnostic algorithm.

Results: All patients positive for rheumatoid factor (RF) and/or cyclic citrullinated peptide (CCP) developed persistent IA, so the added value of PDUS was assessed in the seronegative (RF and CCP negative) group. The probability of IA in a seronegative patient was 6%. The addition of clinical and radiographic features raised the probability of IA to 30% and, with certain ultrasound features, this rose to 94%.

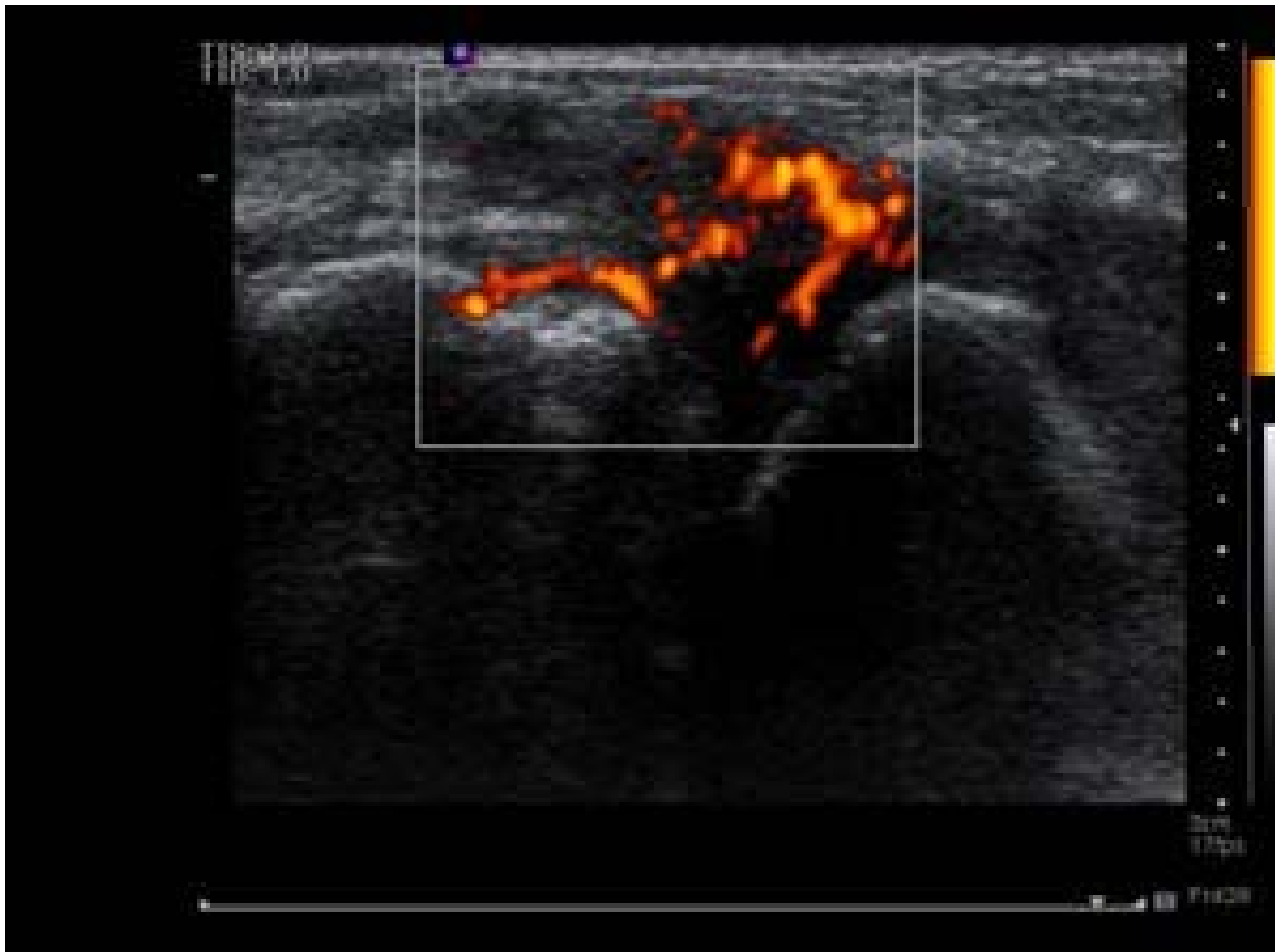
Conclusions: In seronegative patients with early IA, combining PDUS with routine assessment can have a major impact on the certainty of diagnosis.

ultrasound

- Practicality, low (relative) cost, and accessibility in the outpatient, more dynamic
- **Synovitis**
 - Disease activity, response to treatment, inferior detection this with MRI as better jts capture.
 - Predictive erosive changes in RA thought to be in clinical remission (brown et al. AR 58(10) 2958-2967(2008)
- **Tenosynovitis** (especially at the extensor carpi ulnaris may be particularly prominent in early RA
- **Bone erosion** - greater definition of bone surface than Xray, inferior to MRI, more responsive to progression over 12 months than xray.

MRI

- more useful in detection of multiple joints as not technician dependent and changes of u.s can varied.
- Measure of activity with **synovitis**, **bone oedema** (BMO), earlier in detecting **erosion** (MRI erosions correspond to radiographic erosion appearing 2-6 years)
- Synovitis been correlated with subsequent erosion on MRI
- The prognostic of MRI finding in RA is uncertain as meaning regarding long-term outcomes has not yet been established.
- **BMO** appear to indicate microscopic erosion – hence can implies that the destructive process in bone.



MCP jt- Longitudinal ultrasound shows synovitis, neovascularity, and early erosion of metacarpal head. Vascular ingrowth into erosion is also observed
(MRI and ultrasound reveal early signs of rheumatoid arthritis
March 10, 2009 | [MRI](#), [Ultrasound](#), [ECR 2009](#))

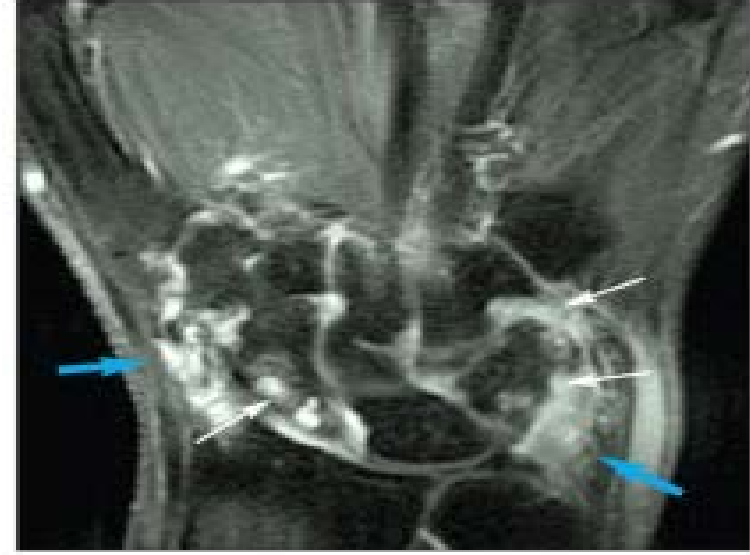
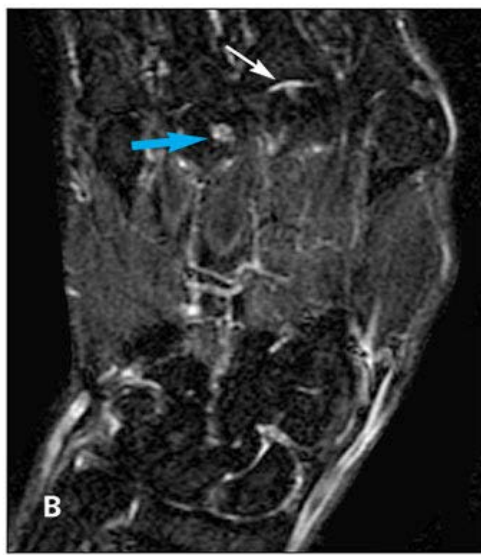


Figure 1 –images show focal erosion in the fourth metacarpal head (blue arrows). A more subtle erosion is seen in the third metacarpal head (thin arrows).

Figure 2 – A coronal postgadolinium-enhanced T1-fat-saturated image shows prominent areas of enhancement at the radioscapoid and ulnocarpal articulations consistent with synovitis (blue arrows). Multiple erosions also are present (thin arrows).



Figure 3 – Diffuse BMO within the triquetrum, lunate, hamate, capitate, trapezoid, and the base of the second metacarpal bones consistent with marrow edema (arrows) are seen in a coronal T2-fat-saturated image.

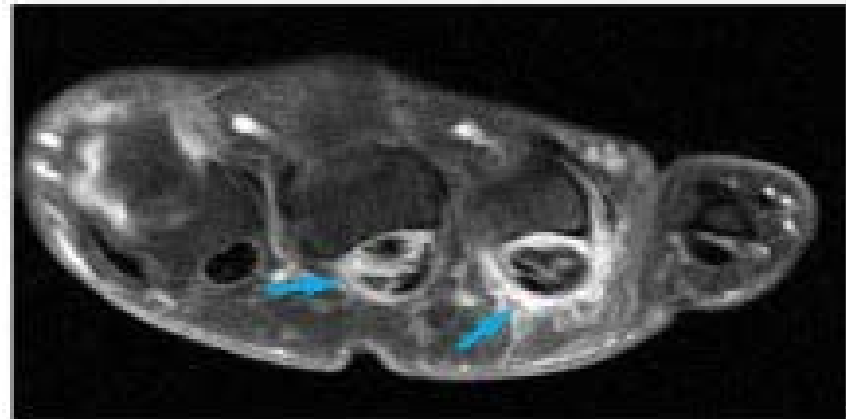


Figure 4 – A postgadolinium-enhanced T1-fat-saturated image in the axial plane shows conspicuous high signal around the third and fourth flexor tendons (arrows), denoting enhancing synovium, which is consistent with tenosynovitis.

Differential diagnosis and potential diagnostic outcomes of undifferentiated inflammatory arthritis

Diagnosis	Sex	Age	Lab tests	Comments
Undifferentiated inflammatory arthritis	F > M	35 to 65	10 to 15% RF+ less frequent ACPA+	Chronic, usually seronegative, inflammatory arthritis, atypical of RA or fails to meet classification criteria for RA. Up to 50% may evolve into RA; up to 25% will go into remission.
Rheumatoid arthritis	F > M	35 to 65	70 to 80% RF+ 70 to 80% ACPA+	Chronic inflammatory polyarthritis, typically meets classification criteria for RA. RA often begins insidiously with vague constitutional and musculoskeletal symptoms that may last up to months before synovitis is evident.
Undifferentiated peripheral spondyloarthritis	M > F	15 to 45	> 50% HLA-B27+	Most often presents as asymmetric large joint involvement with predominantly lower extremity involvement, and often with enthesitis or occasionally dactylitis, as in several forms of SpA. May involve only a few joints. Often "silent" urogenital tract infection (eg, chlamydia).
Psoriatic arthritis	M = F	30 to 55	<20% RF+	Some patients have asymmetric large joint involvement, similar to other SpA. 50% of those with psoriatic arthritis will have an RA-like distribution (MCPs, PIPs, wrists). Cutaneous psoriasis will be evident in the vast majority of cases.
Tophaceous gout	M > F	M: 25 to 70	Usually RF–	Intermittent inflammatory arthritis during the onset, with evolution of tophi and chronic inflammatory polyarthritis. Elevated serum urate and tophi help distinguish from RA.
		F: >45	>95% ↑ serum urate	
Erosive inflammatory osteoarthritis	F > M	>60	Usually RF– (but normally slight increase in RF-positivity with increasing age)	Chronic polyarthritis with intermittent or sustained inflammation affecting PIP and DIP joints. Radiographs demonstrate distinctive erosions and evidence of OA.
Pseudogout	F = M	>60	Usually RF– (but normally slight increase in RF-positivity with increasing age)	5% of patients will have "rheumatoid-like" inflammatory arthritis with stiffness, fatigue, synovitis, and elevated ESR, often lasting four weeks to several months.
Reactive arthritis (formerly known as Reiter's syndrome)	M > F	16 to 50	Usually RF–; 50 to 80% HLA-B27+	Post-infectious SpA; often associated with low back pain, ocular, genitourinary, or GI symptoms and enthesitis (heel pain).
Enteropathic arthritis	M = F	All ages	Usually RF–	Up to 20% of patients with Crohn's disease or ulcerative colitis will develop peripheral arthritis. Diagnosis may be difficult until GI involvement becomes apparent. Associated with oral ulcerations, GI symptoms or other features of SpA.
Systemic lupus erythematosus	F > M	15 to 40	10 to 15% RF+; >95% ANA+ (>80% anti-dsDNA-positive; other characteristic ANA subsets)	Chronic non-deforming inflammatory polyarthritis associated with ANA positivity and other features of SLE.
Polymyositis/ dermatomyositis	F > M	30 to 60	95% RF–; >50% ANA+ (characteristic ANA subsets); >70% ↑ CK	Chronic inflammatory arthritis uncommonly occurs early in course of PM/DM. Features of proximal muscle weakness, bulbar dysphagia, muscle enzyme elevation, or skin involvement (ie, Gottron's papules) should be sought.
Scleroderma	F > M	30 to 50	95% RF–; >90% ANA+ (characteristic ANA subsets)	Chronic inflammatory polyarthritis may predominate over skin changes early in the disease. Associated with Raynaud's phenomenon, sclerodactyly, dysphagia, hypertension, or renal abnormalities.
Sarcoid arthritis	F > M	20 to 40	Usually RF–	15% of patients with sarcoidosis will develop arthritis. Early in the disease a chronic inflammatory oligo or polyarthritis lasting weeks to months may develop and typically involve the ankles and knees. Other features of sarcoidosis (ie, erythema nodosum, hilar adenopathy) are usually

New paradigms in RA Management

- Characteristic

1. Chronic
2. Systemic
3. Tissue damage
4. Aggressive
5. Progressive
6. Biologically complex
7. Focus
8. Collateral damage
9. Management

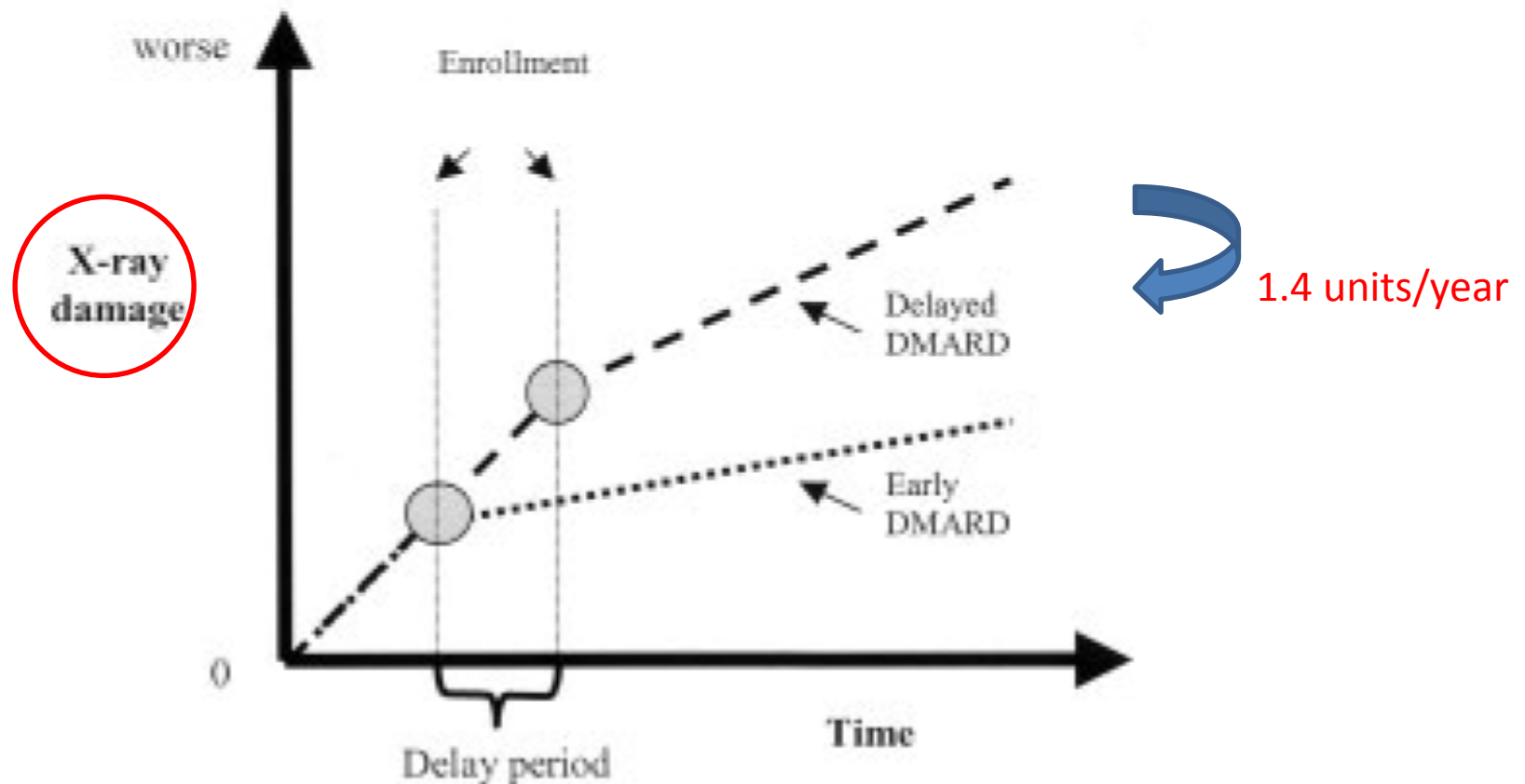
- Modern paradigms

- Lifelong therapy- 'Burden of disease'
- Don't just treat joints
- Prevent Structural Damage
- Early & Intensive therapy
- "Window" of opportunity
- Combination therapy-based on MTX
- Remission or Low Disease Activity
- Zero tolerance inflammation
- Treat to target, T2T

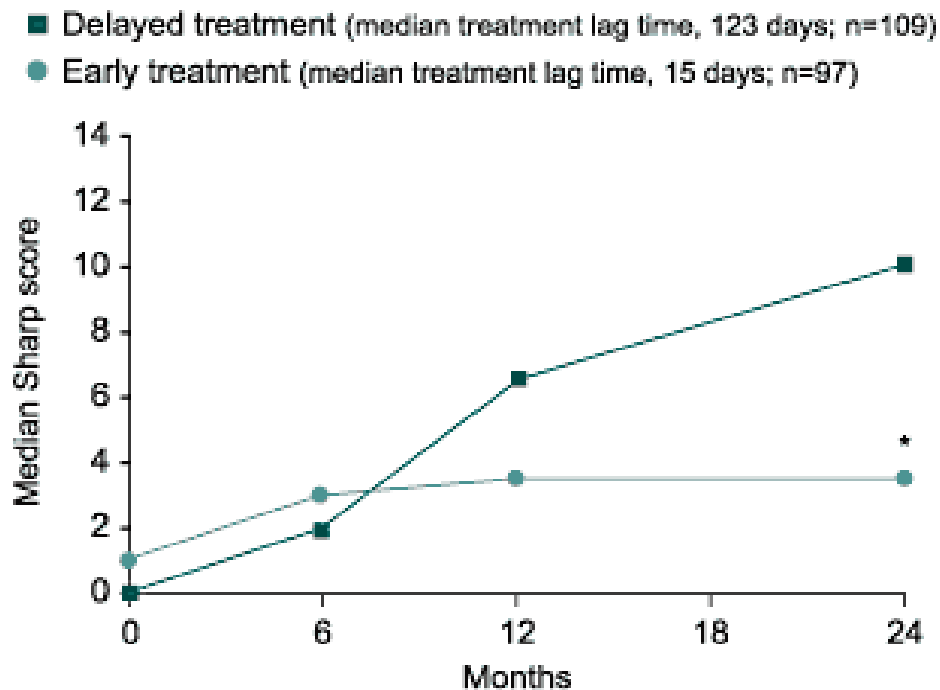
- Adapted from Dr Peter Nash (rheumatologist , Queensland)

Early treatment of Active RA- Impact on Progression Rate of Structural Damage-

Meta-analysis of 12 studies on early vs. delayed initiation of DMARD and corticosteroid therapy

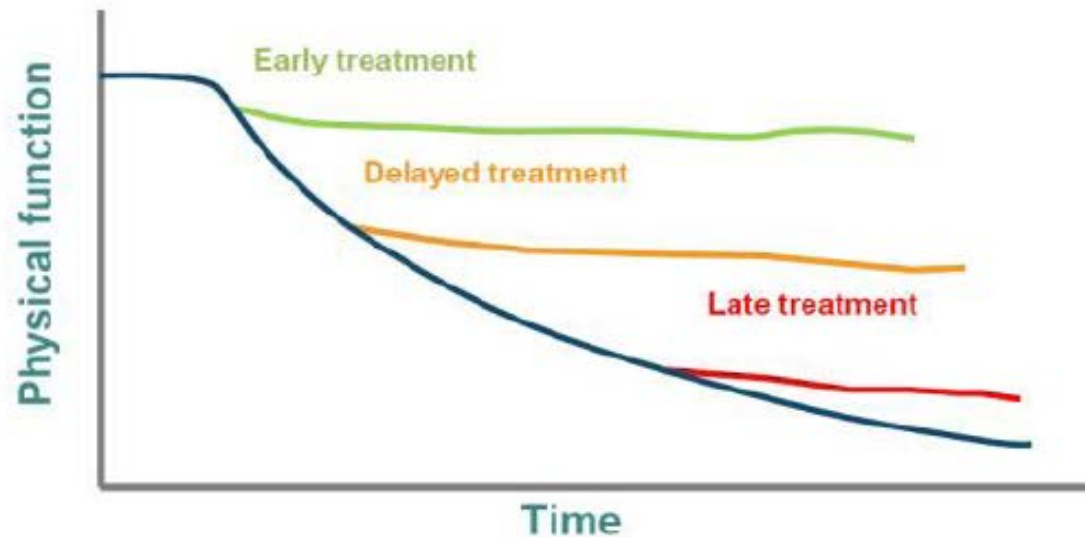


Effects of Early treatment with DMARDs on Radiologic progression



Smolen J. et al ARD, 2005

Early Treatment



- Starting treatment early is preferable, but difficult in clinical practice
- To facilitate early therapy in clinical practice, the patient must:
 - recognise their symptoms early
 - reach a rheumatologist quickly
 - be diagnosed effectively

Many barriers
can prevent this
from occurring

Drug therapy in undifferentiated arthritis: a systematic literature review

K V C Wevers-de Boer, L Heimans, T W J Huizinga, C F Allaart

Ann Rheum Dis 2013;**72**:1436–1444. doi:10.1136/annrheumdis-2012-203165

Treatment UIA

- Same goal – to suppress inflammation in first 3 month, at least 50% reduction in disease activity.
- It cannot be determined at presentation which patients with UA will develop persistent and/or destructive disease
 - (Proposal for a new nomenclature of disease-modifying antirheumatic drugs, Smolen J et al. ARD 2014 Jan;73(1):3-)
- The exact diagnosis at this undifferentiated state is less important than the timely start of a treatment that interferes with the disease process.

Choice of drug regimen with UIA based upon:

The **distribution of the joint** involvement and **serologic testing**, resulting in two clinical categories:

- Disease that generally resembles RA, with prominent upper extremity involvement and/or RF/ACPA +ve (more likely to develop into RA)
- Disease that resembles peripheral SpA, with primarily lower extremity involvement and RF/ACPA –ve
- The response to prior or initial therapies
- The severity of disease

Treatment

- Non- pharmacology - patient education, physical and occupational therapy, smoking cessation.
- Pharmacologic therapy-
 - should follow baseline testing and pre-treatment screening.

UIA treatment

- csDMARD combined with short-term (<six months), low-dose (<10 mg) glucocorticoids, rather than only NSAIDs and glucocorticoids without csDMARDs. (Grade 2B)

- Upper extremity disease or RF/ACPA-positive —
 - suggest treatment with MTX rather than other DMARDs. (Grade 2C)
 - The dose should be gradually titrated up to 20 to 25 mg once weekly to achieve a clinical response.
- The use of MTX in such patients is based upon
 - the resemblance of UIA with these characteristics (UL/seropositive) to RA
 - the likelihood that it will evolve into RA, and the well-established benefits of MTX in RA, where it is the anchor DMARD, including those in whom using biologic DMARDs

Alternative therapies include:

- ●Hydroxychloroquine –
 - very mild disease activity,
 - RF- and ACPA-negative, clinically more like RA than SpA
 - an adjunctive therapy, especially if MTX has induced some improvement for UIA
- ●SSZ
 - Alternative for patients unable or unwilling to take MTX, esp SpA features (**Grade 2C**).
 - RF- or ACPA-positive,
 - The dose should be gradually increased up to usually 2g /maximum of 3g daily.
- ●LEF
 - Suspected future likelihood of RA or PsA is suspected
 - Teratogenic, avoid childbearing

Pregnancy or anticipating pregnancy

- Regardless of the pattern of joint involvement or RF/ACPA result, preferably
 - HCQ, SSZ, given its relative safety during pregnancy (AR 2003, nove;48(11):3207, Am J Gastroenterology 2007,102;1406)
 - Low dose prednisolone (<10mg)
 - Can combined HCQ/SSZ
 - Others : biologic (limited data, anti TNF now category B by FDA)

Rationale for DMARDs in UIA

- **Suppression disease activity and radiographic progression-**

- suggested on 2013 systematic review identified several randomized trials, open-label studies, and cohort studies, (included ERA) - Drug therapy in UIA: a systematic literature review. Wevers-de Boer KV et al. ARD 2013 Sep;72(9):1436-44.

- **Mays delay but not prevent development of RA**

- One randomized suggested that treatment with MTX, compared with placebo.
- 110 patients, MTX (15-30mg) for 12/12 and 18/12 follow-up, half of MTX did not meet the criteria in 1 yr vs placebo
- subgroup analysis ACPA +ve show statistically significant benefit of MTX
- 40% (55) vs 53% (29) in each group progress to RA
- (Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. van Dongen H, et al AR. 2007;56(5):1424.)

Rationale for DMARDs in UIA

- RCT support the long-term benefits of early intervention with DMARDs **in limiting progression of disease in patients with RA**, further supporting the likely benefit of these approaches in UIA
 - (Repair of erosions occurs almost exclusively in damaged joints without swelling. Lukas C et al. ARD. 2010 May;69(5):851-5)
- The **risks of MTX/SSZ are generally modest**, with many decades of experience in the use of these agents and in the monitoring, prevention, and management of their risks
- **MTX is effective with 61% remission** in 4/12 (610 ERA/UIA patients) A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study, Heimans L et al. ARD 2014;73(7):1356.
- Early treatment more **likely of drug free remission** (32% in 1 year, tapered off mTX after 8 months in in remission)
- **Reduction in cardiovascular risk in RA cohorts**
 - (Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study ., Choi HK et al , Lancet. 2002;359)

MONITORING

- Using the same approach as for patients with RA.
 - disease activity
 - TSJ, T2T- LDA/remission (DAS 28>than 5.1 active, MDA>3.2-5.1 disease, < 3.2 LDA, <2.6 remission)
 - Drug toxicity
 - Side effects, regular blood monitoring
 - Complication- CVD, osteoporosis, malignancy



Very Well 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 Poor

Your Name _____ Date of Birth _____ Today's Date _____

Provider Global Assessment of Disease Activity

Very Well 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 Poor

How to Score the CDAI

Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
Add the above values to calculate the CDAI score	(0-76)	

CDAI Score Interpretation	
0.0 – 2.8	Remission
2.9 – 10.0	Low Activity
10.1 – 22.0	Moderate Activity
22.1 – 76.0	High Activity

Bitte kreuzen Sie die Antwort an, die am besten Ihre Fähigkeiten während der letzten Woche beschreibt.

	OHNE jede Schere- r gleich	Mit GROSSE Schere- r gleich	Mit GROSSE Schere- r gleich	Nicht dazu in der Lage	Berechnung
1 Ankleiden und Körperpflege					
Können Sie sich ankleiden, inkl. Binden von Schnürsenkeln und Schließen von Knöpfen?	0	1	2	3	Höchster Wert Frage 1: <input type="text"/>
Können Sie sich die Haare waschen?	0	1	2	3	+
2 Aufstehen					
Können Sie von einem Stuhl ohne Armliehen aufstehen?	0	1	2	3	Höchster Wert Frage 2: <input type="text"/>
Können Sie sich ins Bett legen und wieder aufstehen?	0	1	2	3	+
3 Essen und Trinken					
Können Sie Fleisch schneiden?	0	1	2	3	Höchster Wert Frage 3: <input type="text"/>
Können Sie eine volle Tasse oder ein volles Glas zum Mund führen?	0	1	2	3	
Können Sie eine neue Milchküpe öffnen?	0	1	2	3	+
4 Gehen					
Können Sie im Freien auf ebenem Gelände gehen?	0	1	2	3	Höchster Wert Frage 4: <input type="text"/>
Können Sie fünf Treppenstufen hinaufsteigen?	0	1	2	3	oder:
Bitte kreuzen Sie alle HILFSMITTEL an, die Sie üblicherweise benutzen:					Wert Frage 4 wenn Hilfsmittel oder Treppen angegeben wurden und höchster Wert 0 oder 1 beträgt: <input type="text"/>
<input type="checkbox"/> Hilfsmittel zum Ankleiden (Knöpfhaken, Reißverschluss- hilfe, verlängelter Schuhbrette)	<input type="checkbox"/> Gehesagen				
<input type="checkbox"/> Spezialstuhl oder erhöhter Stuhl	<input type="checkbox"/> Krücken				
<input type="checkbox"/> besondere Hilfsmittel beim Essen und Trinken	<input type="checkbox"/> Rollstuhl				
<input type="checkbox"/> Stock	<input type="checkbox"/> andere, bitte angeben:				
Bitte kreuzen Sie die Beschreibung an, bei denen Sie geschwindlich VON EINEM ANDEREN MENSCHEN benötigen:					Summe Punkte Seite 1: <input type="text"/>
<input type="checkbox"/> Ankleiden und Körperpflege	<input type="checkbox"/> Essen und Trinken				
<input type="checkbox"/> Aufstehen	<input type="checkbox"/> Gehen				

Fortsetzung auf Seite 2

Prognosis

- Varied with study results
 - Remains UIA in 21-87% after 1 years follow-up.
 - Diagnosed as RA (13-55%)
 - Osteoarthritis (baseline 0-16%)
 - Others (6-20%)
- ≈10 to 40 % experienced spontaneous remission within one year
 - this proportion was not increased by treatment with glucocorticoids

Table 1 Predictors of erosive rheumatoid arthritis

Table 1 Predictors of erosive rheumatoid arthritis		
Type of marker	Parameter	Prone to fluctuation or alteration by treatment?
Serological	Elevated CRP level	Yes*
	Elevated ESR	Yes*
Clinical	Swollen joint count	Yes*
	Tender joint count	Yes*
	Extra-articular manifestations (e.g. rheumatoid nodules, Sjögren's syndrome, rheumatoid vasculitis, Felty syndrome and rheumatoid lung disease)	In part
Immunological	Presence of rheumatoid factor	No†
	Presence of anti-CCP antibodies	No†
Genetic	HLA-DR4 shared epitope	No†
	<i>IL4R</i> Ile50Val single nucleotide polymorphism	No†
Radiological	Bone marrow edema (MRI)	Yes*
	Bone erosions (X-ray)	No
*Indicative of inflammatory disease activity. †Stable over time and characteristic of an individual patient's disease. Abbreviations: CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.		

Skapenko, A. *et al.* (2009) Prognostic factors in rheumatoid arthritis in the era of biologic agents
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2009.157

In McGill, one centre referral result

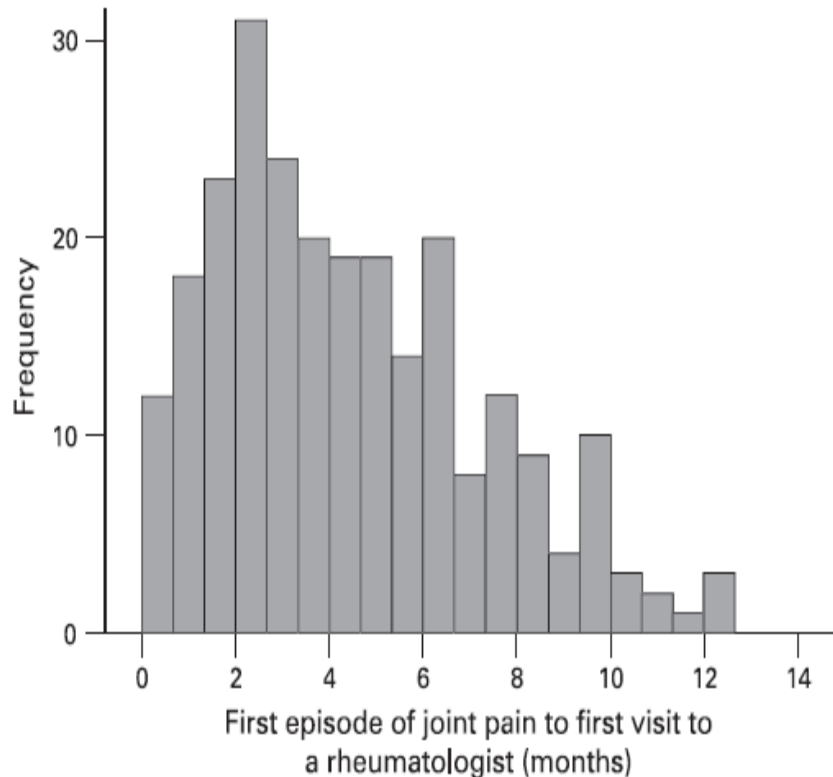


Figure 1 Time between onset of arthritis symptoms and first visit to a rheumatologist.

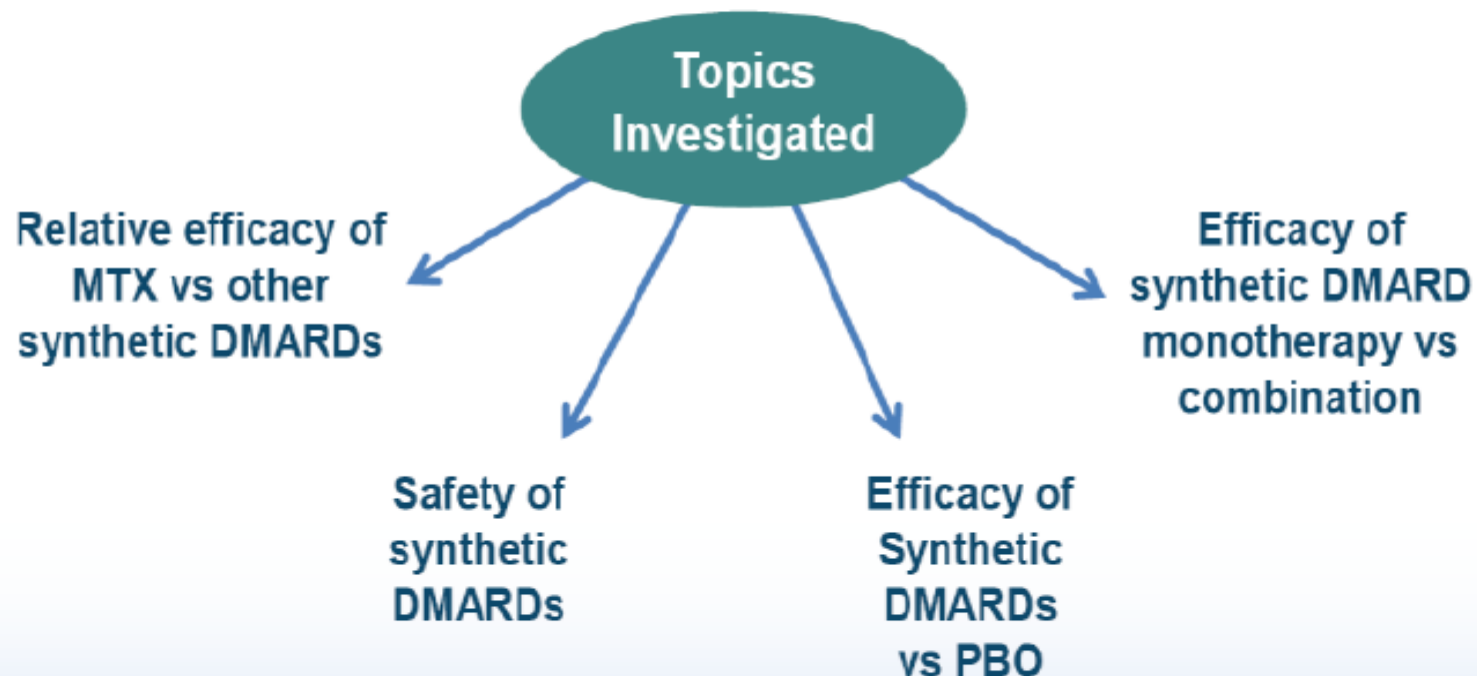
- **Challenges**
- Facilitate rapid referral with defined criteria
 - >3swollen joints,
 - MTP/MCP involvement
 - EMS >30 mins
 - (Smolen J, ARD 2002, 61:290)
- Early arthritis clinic
- **Immediate access clinic**

Why Methotrexate the anchor Drugs for RA ?

And the EULAR recommendation
emphasis this??

Synthetic DMARDs – A Systematic Review

- A systematic review was conducted to ascertain the level of evidence supporting the role of synthetic DMARDs in the treatment of RA
- 97 RCTs, with a total of 14,159 patients, were included in the analysis.



EULAR Recommendations - Synthetic DMARDs

3. MTX should be part of the first treatment strategy in patients with active RA

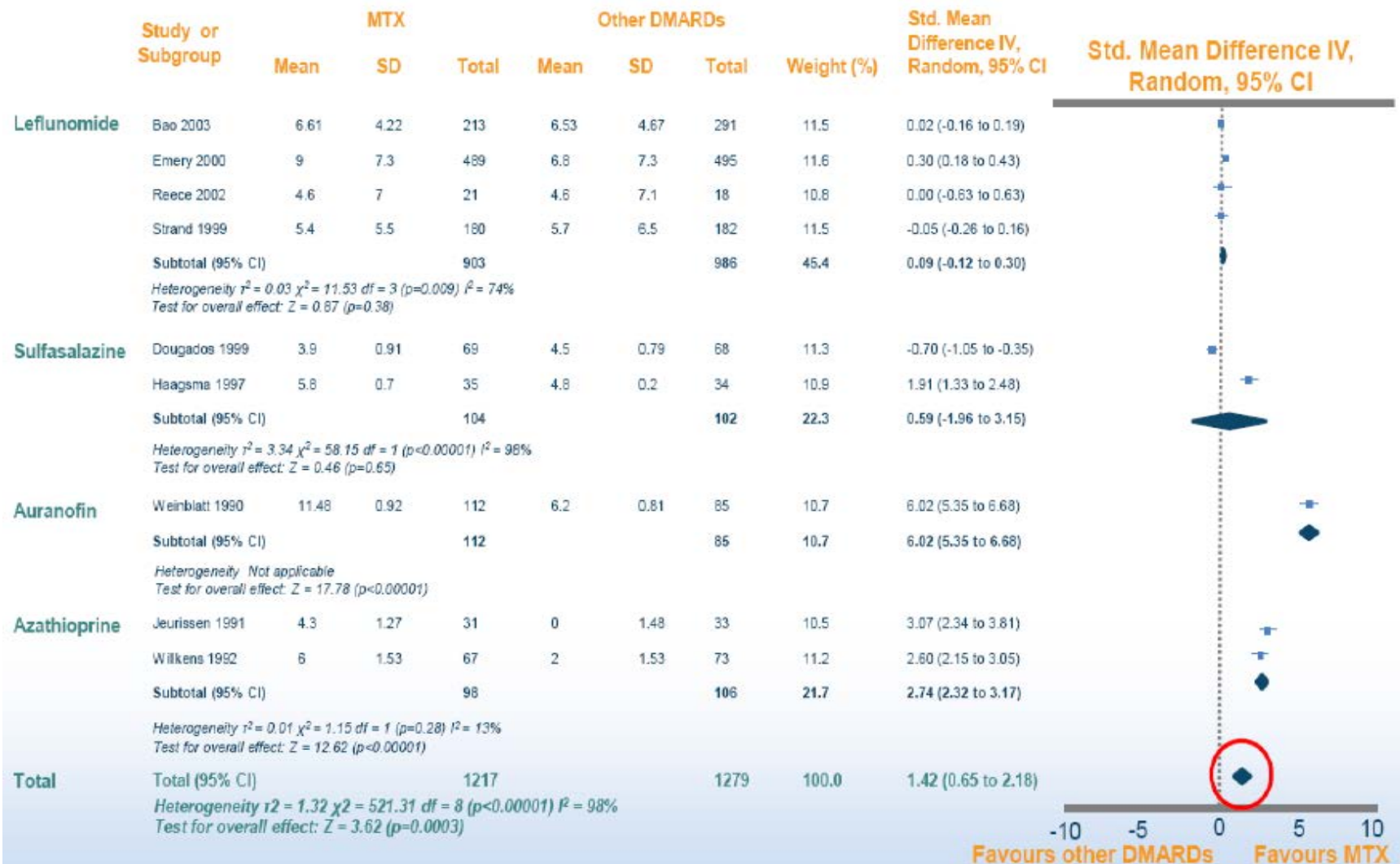


Table 2 The 2016 EULAR updated recommendations

Overarching principles

- A Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
- B Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues
- C Rheumatologists are the specialists who should primarily care for patients with RA
- D RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist

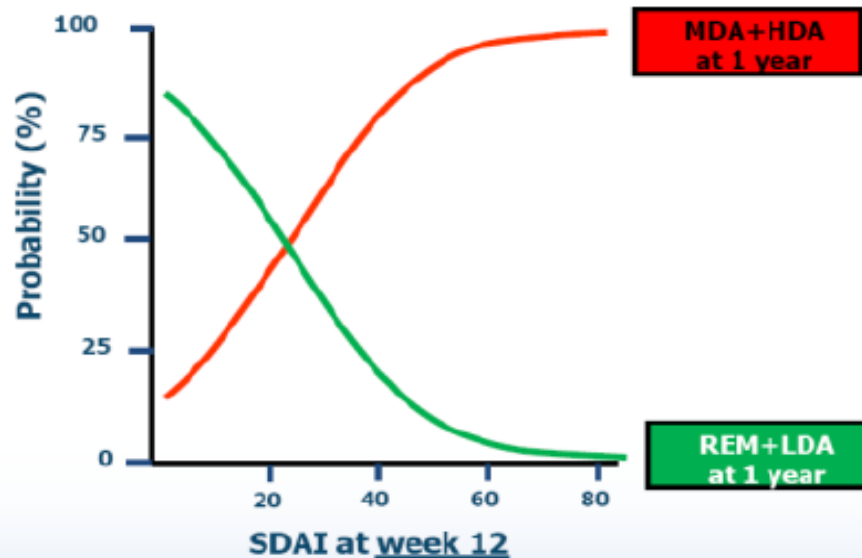
Recommendations

- 1. Therapy with DMARDs should be started as soon as the diagnosis of RA is made
- 2. Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient
- 3. Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted
- 4. MTX should be part of the first treatment strategy
- 5. In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy

Rapid Adaptation

Evidence suggests that assessment and adaptation every 3 months is important for achieving targets

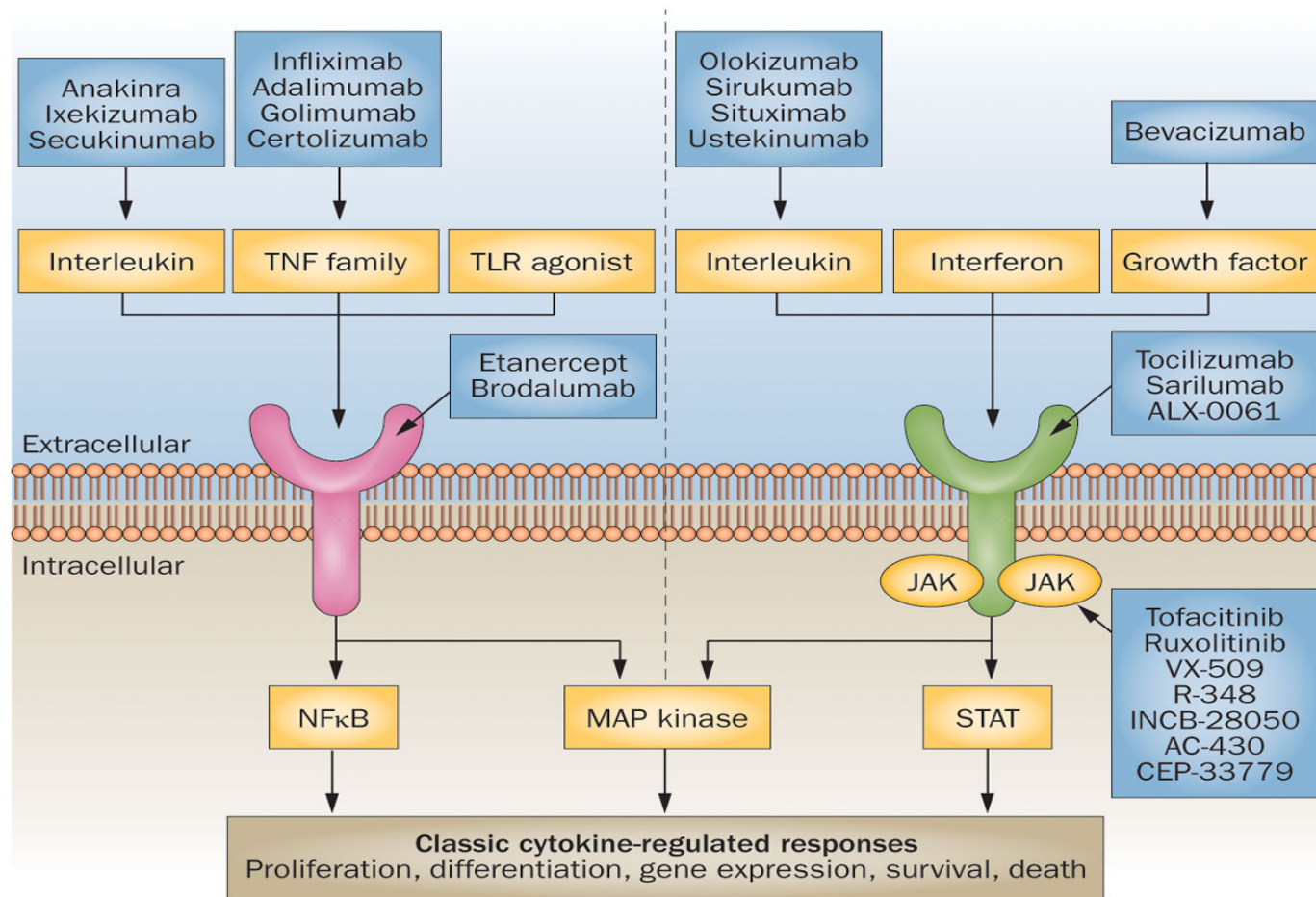
- the probability of achieving remission at 1 year has been shown to be strongly linked to the week 12 SDAI response



- TICORA provides evidence for the success of a similar strategy with synthetic DMARDs in early RA patients

6. Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible
7. If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered
8. If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, addition of a bDMARD^{*1,2} or a tsDMARD^{*3} should be considered; current practice would be to start a bDMARD⁵
9. bDMARDs^{*1,2} and tsDMARDs^{#3} should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs
10. If a bDMARD^{*} or tsDMARD⁵ has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or an agent with another mode of action
11. If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD
12. If a patient is in persistent remission, tapering the csDMARD could be considered

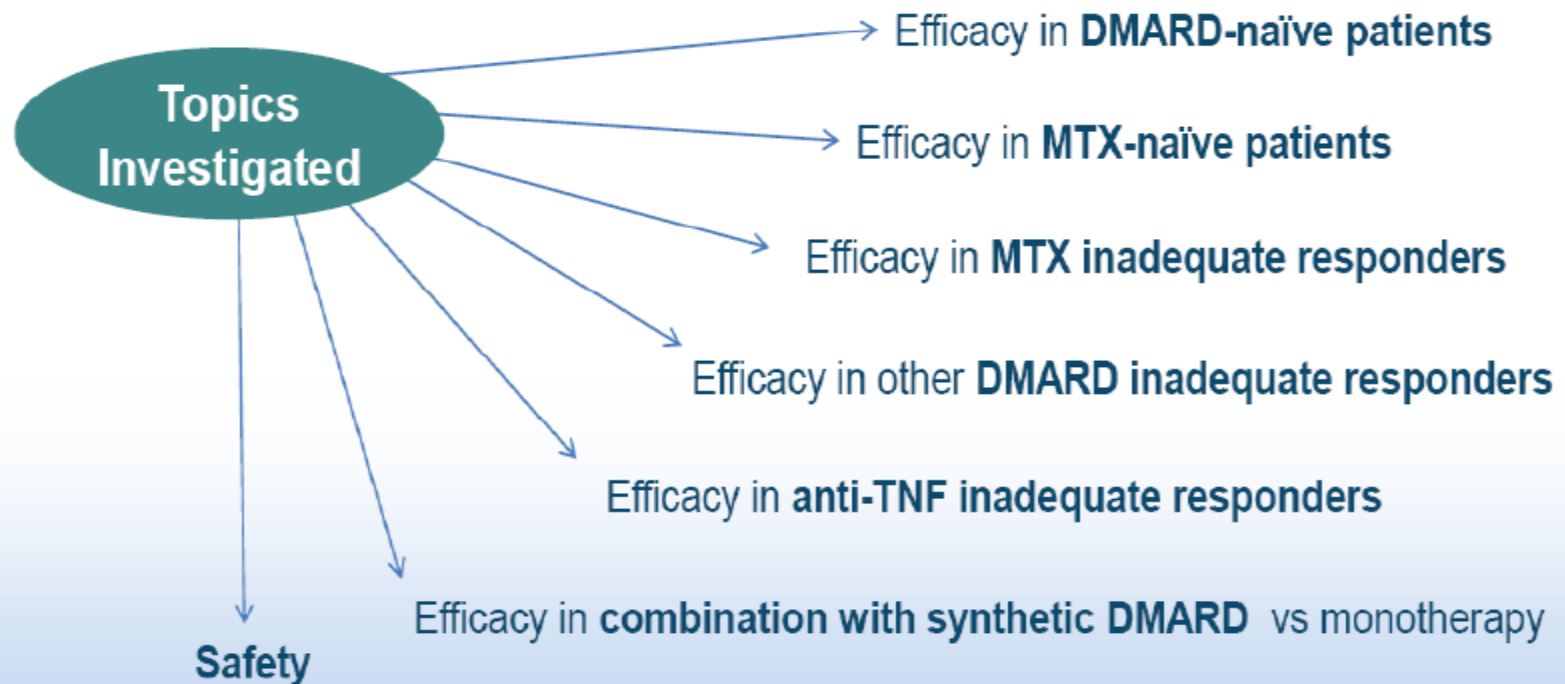
Figure 3 Cytokines and their signalling pathways: different cytokines use different intracellular signalling pathways



Choy, E. H. *et al.* (2013) The problem of choice: current biologic agents and future prospects in RA
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2013.8

Biological DMARDs – A Systematic Review

- A systematic review was conducted to ascertain the level of evidence supporting the role of biological DMARDs in the treatment of RA
- Double blind RCTs in RA patients using at least 1 DMARD were used. Studies had to be ≥ 6 months study duration, written in English and had to contain at least 50 patients
- 87 articles and 40 abstracts fulfilled the criteria



Efficacy in MTX-Naïve Patients

ACR response at 12 Months
Biologic + MTX combination therapy
Relative Risk Ratios vs MTX
Monotherapy

	ACR20	ACR50	ACR70
ABT	NA [†]	1.36	1.57
ADA	1.19	1.26	1.56
ETN	1.34	1.51	1.78
GLM*	1.25	1.31	NA [†]
IFX	1.20	1.50	1.65

* GLM Data at 6 months; † Not available

ACR response at 12 Months
Biologic monotherapy
Relative Risk Ratios vs MTX
Monotherapy

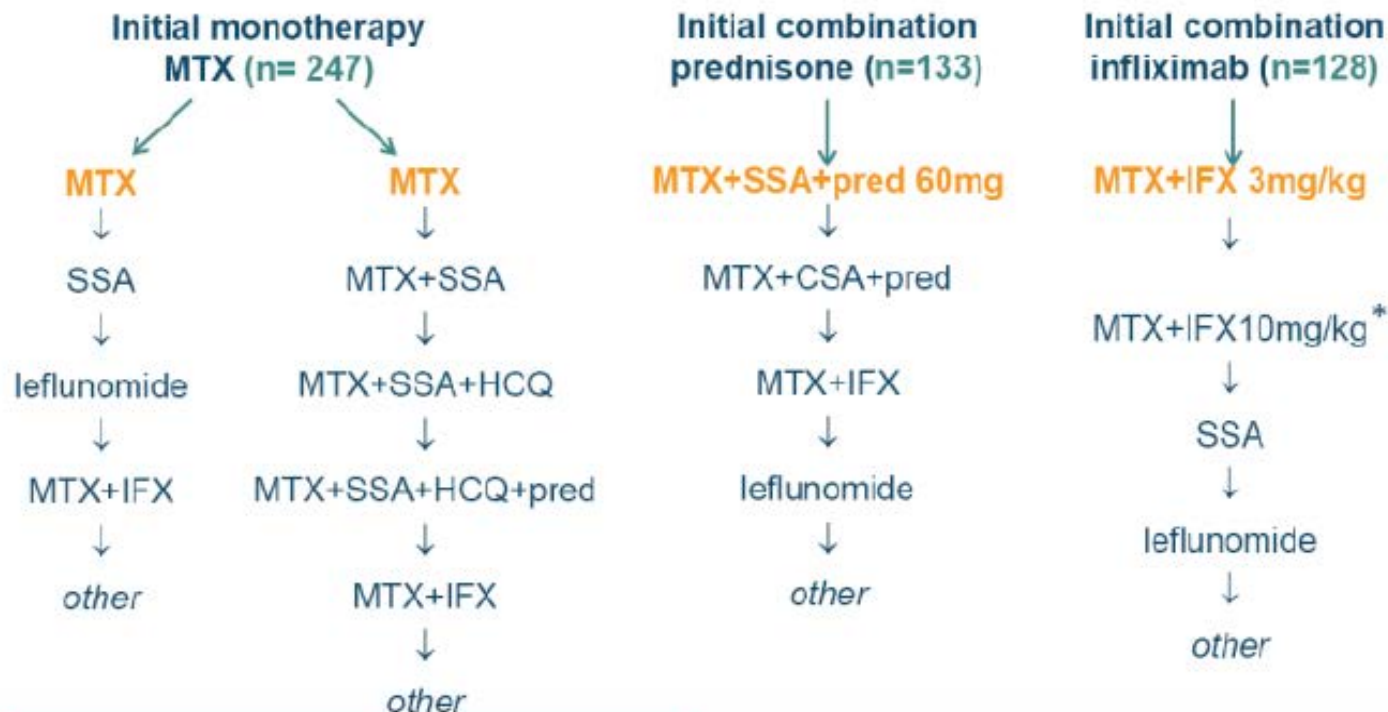
	ACR20	ACR50	ACR70
ADA	0.87	0.89	0.92
ETN	1.22	NA [†]	NA [†]
GLM*	1.04	1.1	NA [†]

* GLM Data at 6 months; † Not available

In monotherapy, ADA and ETN overall RR= 0.98.
 The result were similar in biologic and MTX mono gp

In MTX naive patient, biologic DMARD IFX, ETN, ADA, GLM or ABT
 have been shown to improve clinical outcome (Ib)

Treatment Strategy in BeSt



Initially:

DAS >2.4: next treatment step

DAS ≤2.4 (>6 months): taper to maintenance dose monotherapy

From 3rd year:

DAS <1.6 (≥ 6 months): taper to 0

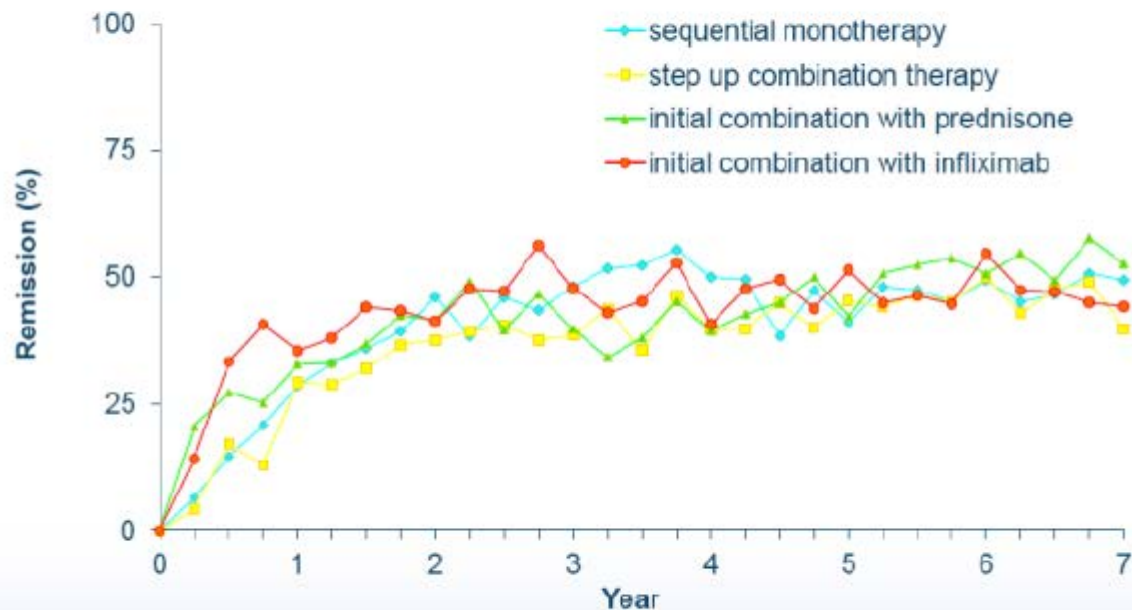
DAS ≥1.6: restart last monotherapy

* IFX 10 mg/kg is not an approved dose

Long Term Data for BeSt

Aim to keep remission

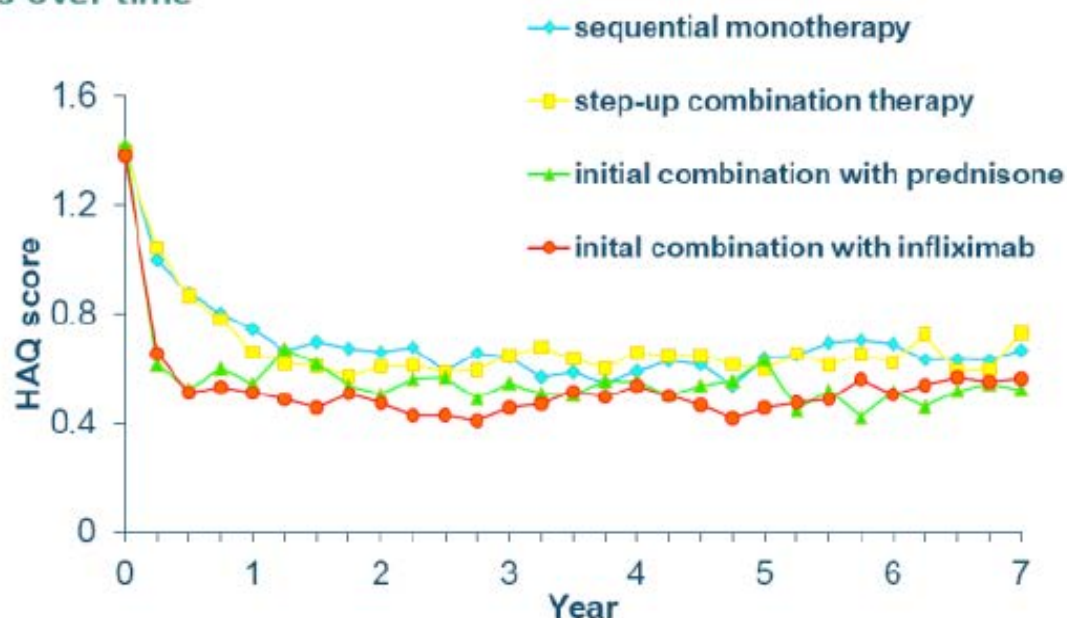
Percentage of patients in remission over 7 years



- 15-16% of patients in each group were in drug-free remission after 7 years

Long Term Data for BeSt

HAQ scores over time



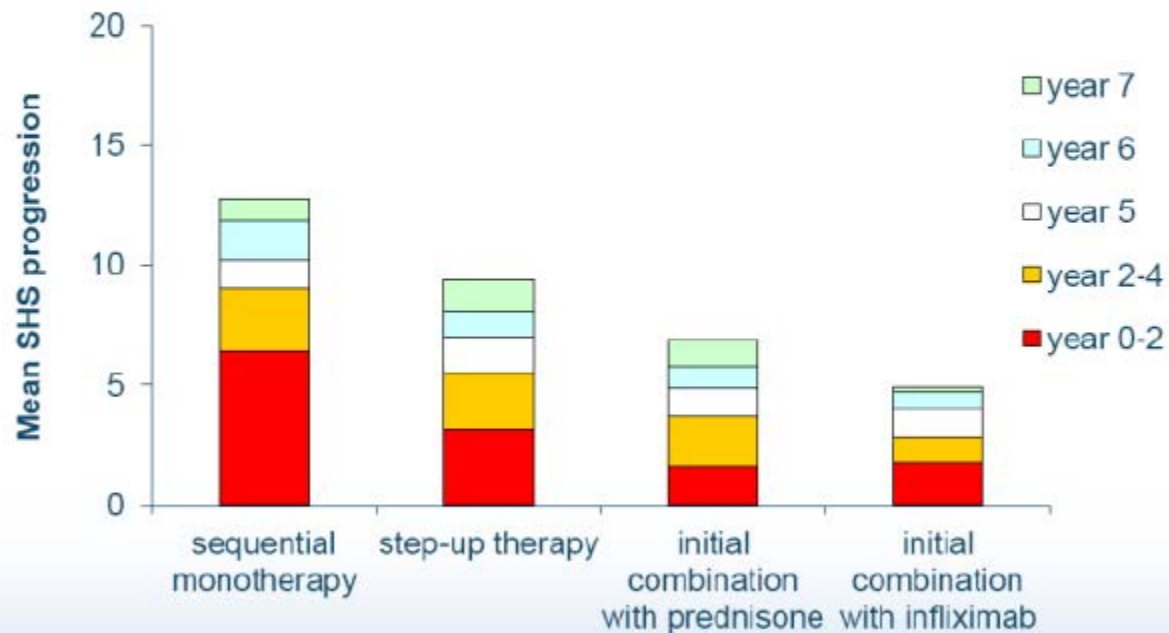
- Improvements in physical functioning are mirrored by good 7 year radiographic outcomes, particularly for those receiving IFX first
- Toxicity and safety between treatment regimens is similar if the most effective treatment comes first

Longitudinal data analysis:
group 4 vs. 1, 2 and 3: $p < 0.05$; group 3 vs. 1 and 2: $p < 0.001$

Klarenbeek et al. Ann Rheum Dis. 2011;70:1039-1046
Unpublished data

Long Term Data for BeSt

Degree of radiologic progression is determined in the first 5 years



BeSt Matrix Model Early RA

Initial monotherapy

CRP (mg/L)	RF and ACPA			Erosions (number)
	-/-	+/- or -/+	+/+	
≥35	47	69	78	≥4
	24	44	56	1-4
	19	37	49	0
10-35	22	42	54	≥4
	9	20	29	1-4
	7	16	23	0
<10	16	32	43	≥4
	6	14	21	1-4
	5	11	17	0

Risk of Rapid Radiographic Progression (%)



Initial combination with prednisone

CRP (mg/L)	RF and ACPA			Erosions (number)
	-/-	+/- or -/+	+/+	
≥35	15	30	42	≥4
	6	13	20	1-4
	4	10	16	0
10-35	5	12	19	≥4
	2	5	8	1-4
	1	4	6	0
<10	4	8	13	≥4
	1	3	5	1-4
	1	2	4	0

Initial combination with IFX

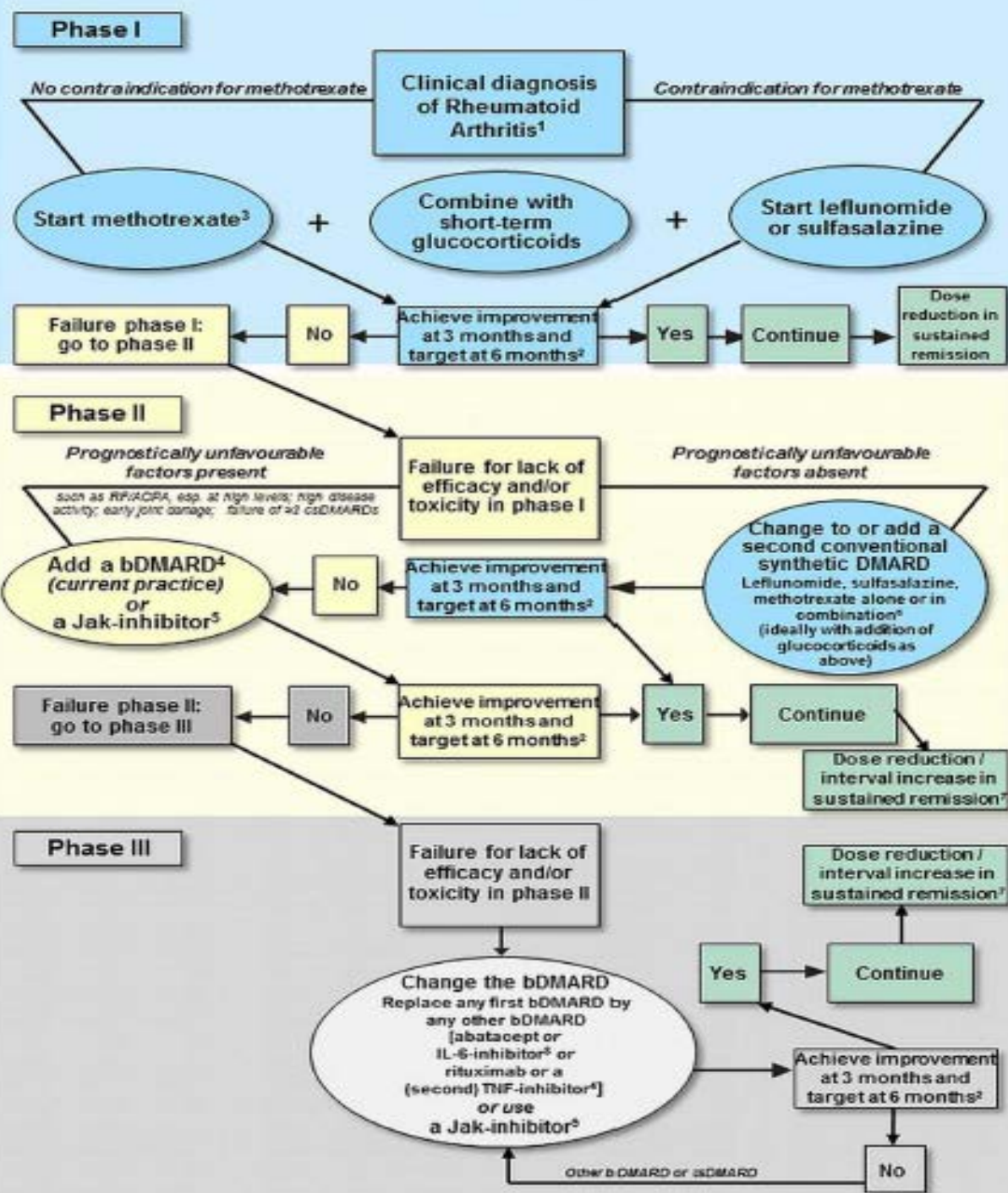
CRP (mg/L)	RF and ACPA			Erosions (number)
	-/-	+/- or -/+	+/+	
≥35	11	24	34	≥4
	4	10	15	1-4
	3	8	12	0
10-35	4	9	14	≥4
	1	3	6	1-4
	1	3	4	0
<10	3	6	10	≥4
	1	2	3	1-4
	1	2	3	0

Overview and analysis of treat-to-target trials in rheumatoid arthritis reporting on remission

M.S. Jurgens¹, P.M.J. Welsing^{1,2}, J.W.G. Jacobs¹

Results. *Thirteen studies were found, 4 comparing effects of tight control to those of usual care, 1 comparing the effects of 2 strategies with the same DMARDs but using different treatment targets, and 8 comparing the effects of tight control strategies with different DMARDs but with the same treatment target. Remission rates differed over a wide range in these studies, but in general were not higher in studies applying a biological DMARD from start compared to studies with initial conventional DMARD strategies. The meta-analysis of the 4 studies comparing tight control versus usual care shows that applying a treat to (any) target strategy appeared to approximately double the remission rates of the participating early RA patients.*

Conclusion. *The trials comparing tight control arms show in general that the more intensive the strategy, the more strict the treatment aim and the more tight the tight control, the better the remission rates. It does not appear obligatory to start with a biological DMARD to get good results in tight control studies.*



Summary

- Inflammatory arthritis has wide differential with some clinical diagnostic difficulty.
- UIA is diagnosis of exclusion made in patients with inflammatory arthritis not fulfilling a defined diagnostic criteria.
- UIA need at least one clinically swollen joint.
- Treatment are usually very similar to RA depend of characteristic of the arthritis and serology finding.
- Earlier treatment will result in clinical benefit.

Thank you...