

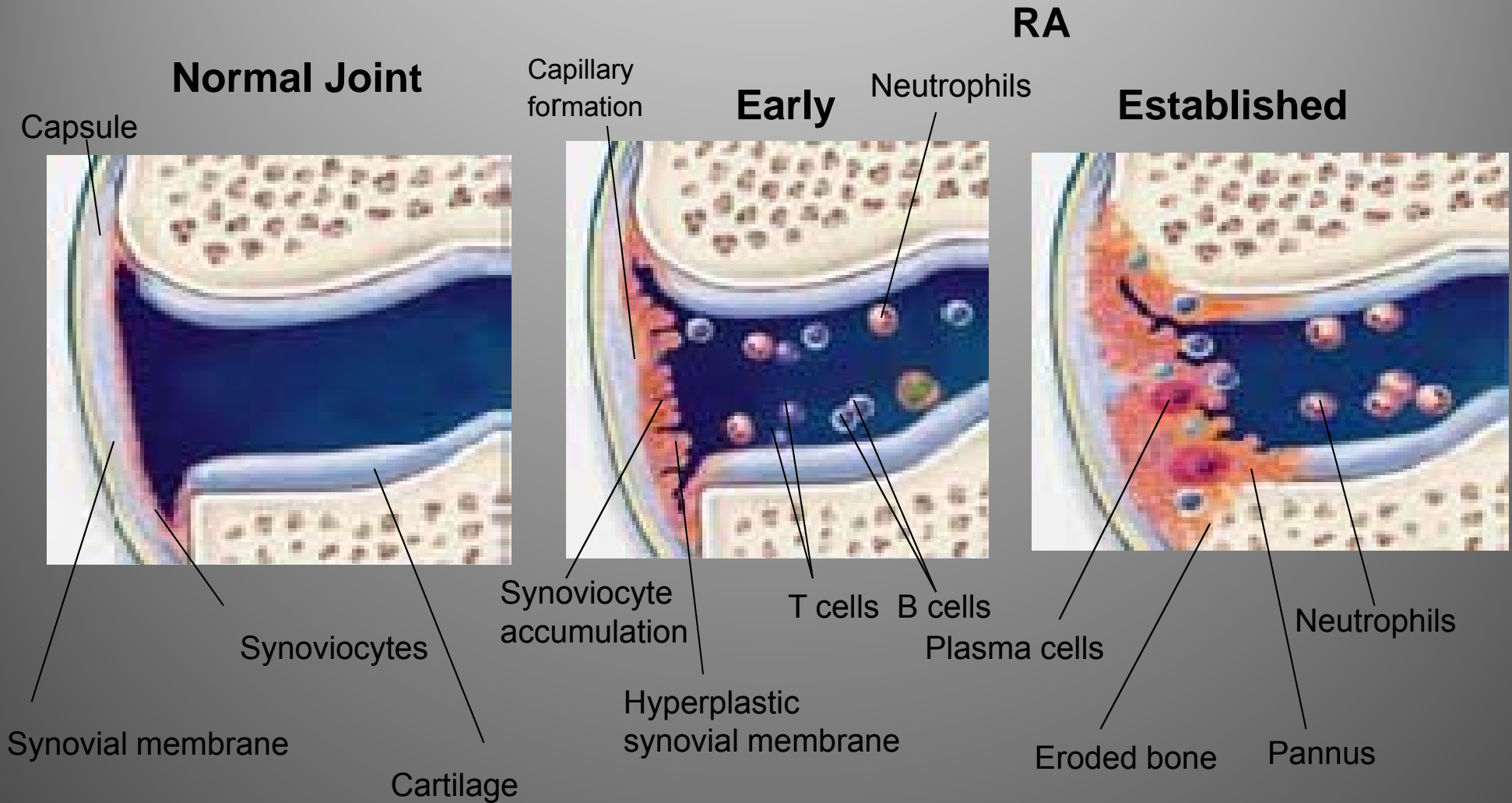
Primary Care Diagnosis and Management of Rheumatoid Arthritis

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Objectives

- Understand the diagnosis and clinical signs of RA
- Develop an approach to selecting disease modifying antirheumatic drugs (DMARDs) prior to referral
- Describe the benefits of prompt treatment of RA

RA Pathophysiology



RA Pathology and Clinical Manifestations

Normal Synovium



RA Synovium



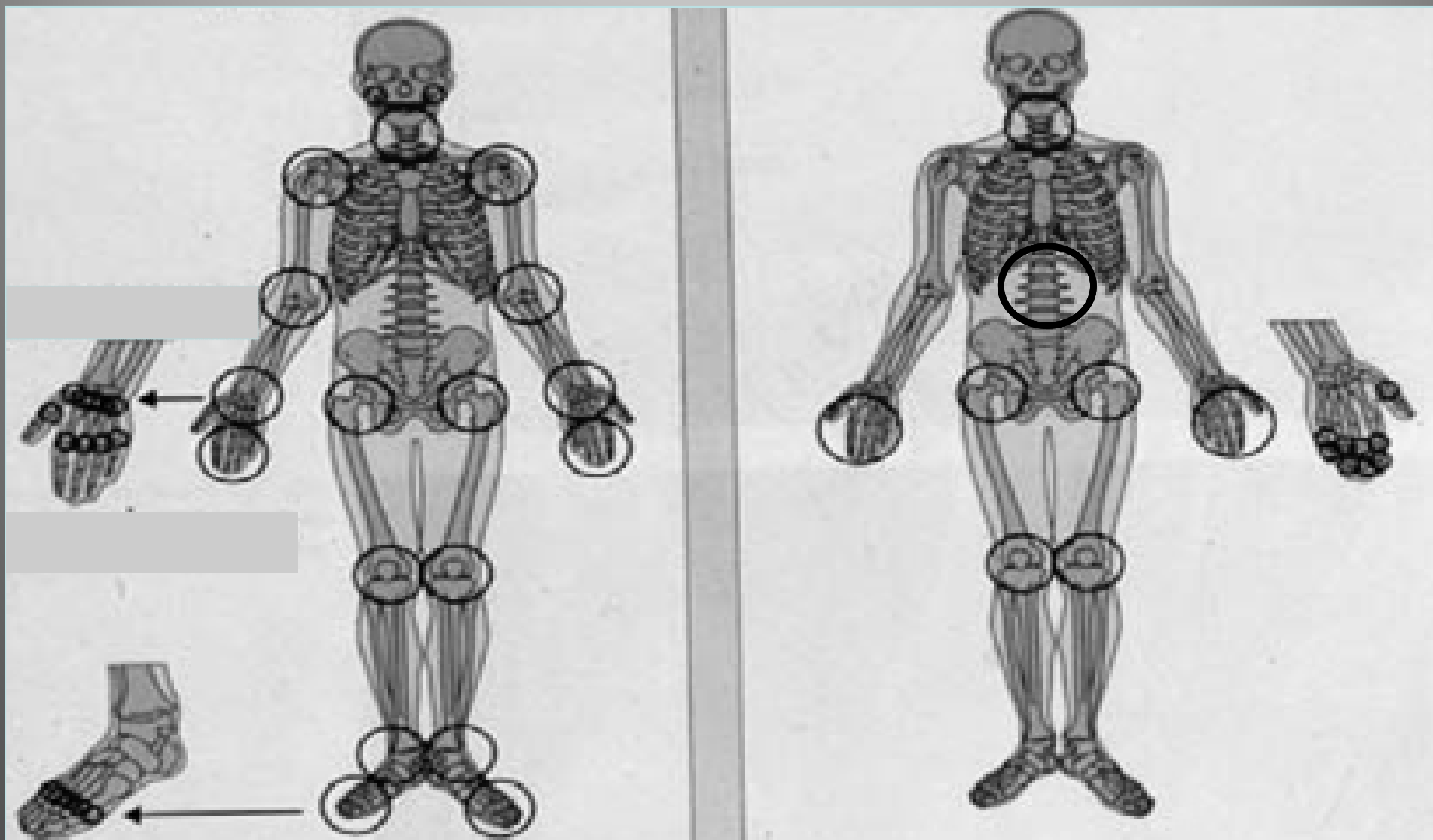
ACR Criteria: Diagnosis of RA

- AM STIFFNESS (>1 h)
- INFLAMMATORY ARTHRITIS OF ≥ 3 JT AREAS
- INFLAMMATORY ARTHRITIS OF HAND JTS
(wrist MCP PIP)
- SYMMETRIC ARTHRITIS
- RHEUMATOID NODULES
- SERUM RHEUMATOID FACTOR OR ANTI-CCP
- RADIOGRAPHIC CHANGES TYPICAL OF RA
(erosions)
- **FOR ≥ 6 WKS**
- **Any 4 = rheumatoid arthritis**
- **Sensitivity: 71-90% Specificity: 90-100%**

Physical Examination

Rheumatoid

Osteoarthritis



Physical Examination

- Joint count of actively inflamed joints



Physical exam



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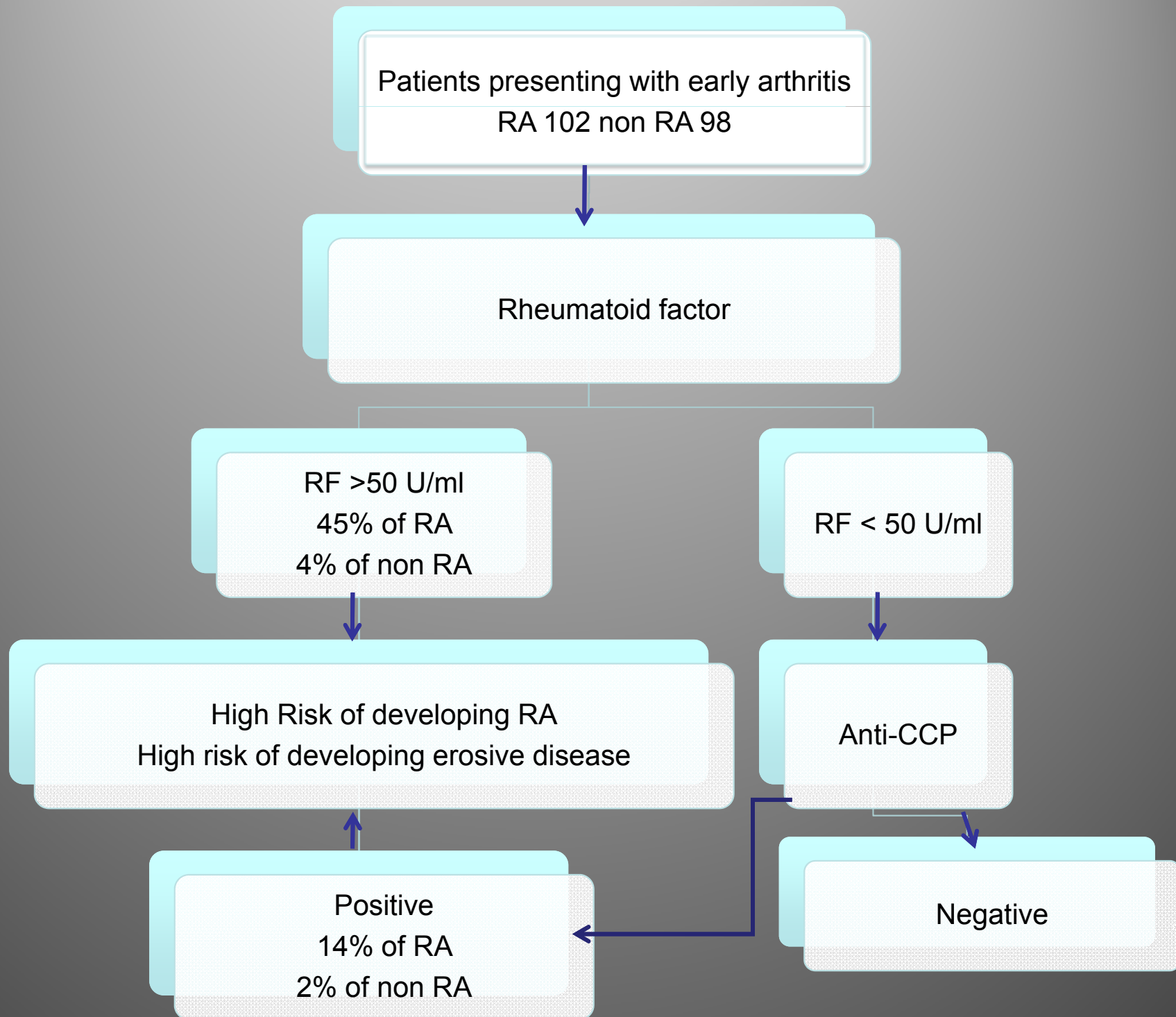
Laboratory and Radiology

- Rheumatoid factor: IgM against Fc of IgG
- Anti-cyclic citrullinated peptide (anti-CCP)
- HCV ab
- ESR or CRP
- CBC, electrolytes, creatinine
- LFTs
- Synovial fluid analysis
- Urinalysis
- Radiographs of hands and/or feet

Serologic Factors in RA: Anti-CCP and RF

Table 1 Diagnostic Value of RF and anti-CCP Data in the overall patient population.

Autoantibodies	RA (n=102)	Non-RA (n=98)	Sensitivity (%)	Specificity (%)	PPV (%)
RF (> 20 U/ml)	56	11	55	89	84
High titer RF (>50 U/ ml)	46	4	45	96	92
Anti-CCP	42	2	41	98	96







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A

B

C

Stages of RA

Early



Intermediate



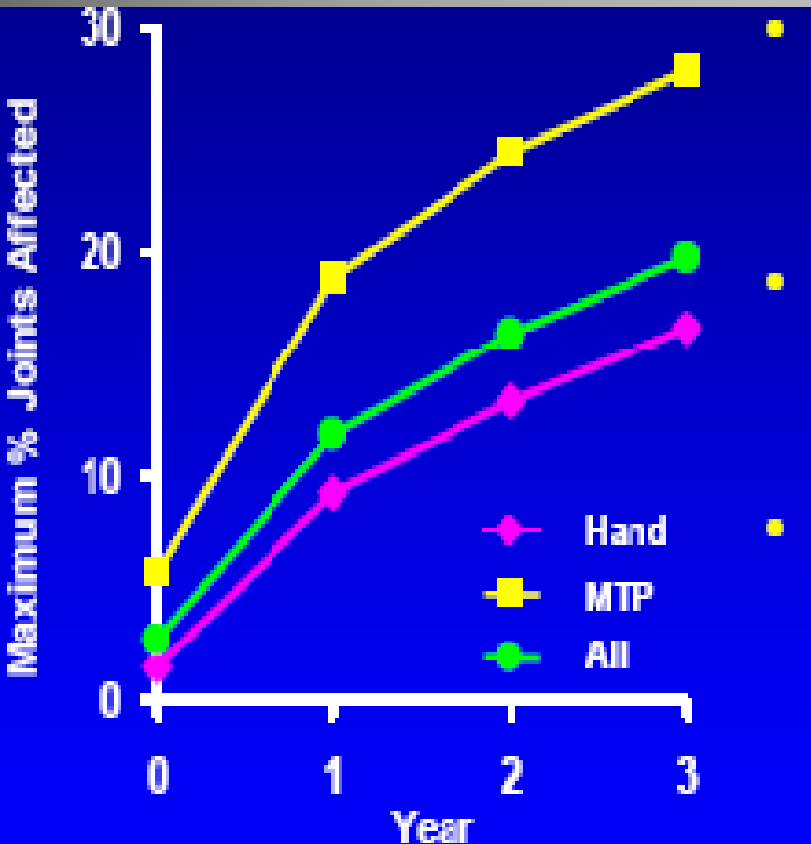
Late



Poor Prognostic Indicators

- Earlier age at onset; female sex
- Polyarticular synovitis
- High titer rheumatoid factor and/or anti-CCP
- Elevated ESR or CRP level
- Erosions or cartilage loss on x-ray (in < 1 yr)
- HLA-DR4
- Poor functional status
- Extraarticular manifestations: rheumatoid nodules, scleritis, ILD, pericarditis, vasculitis

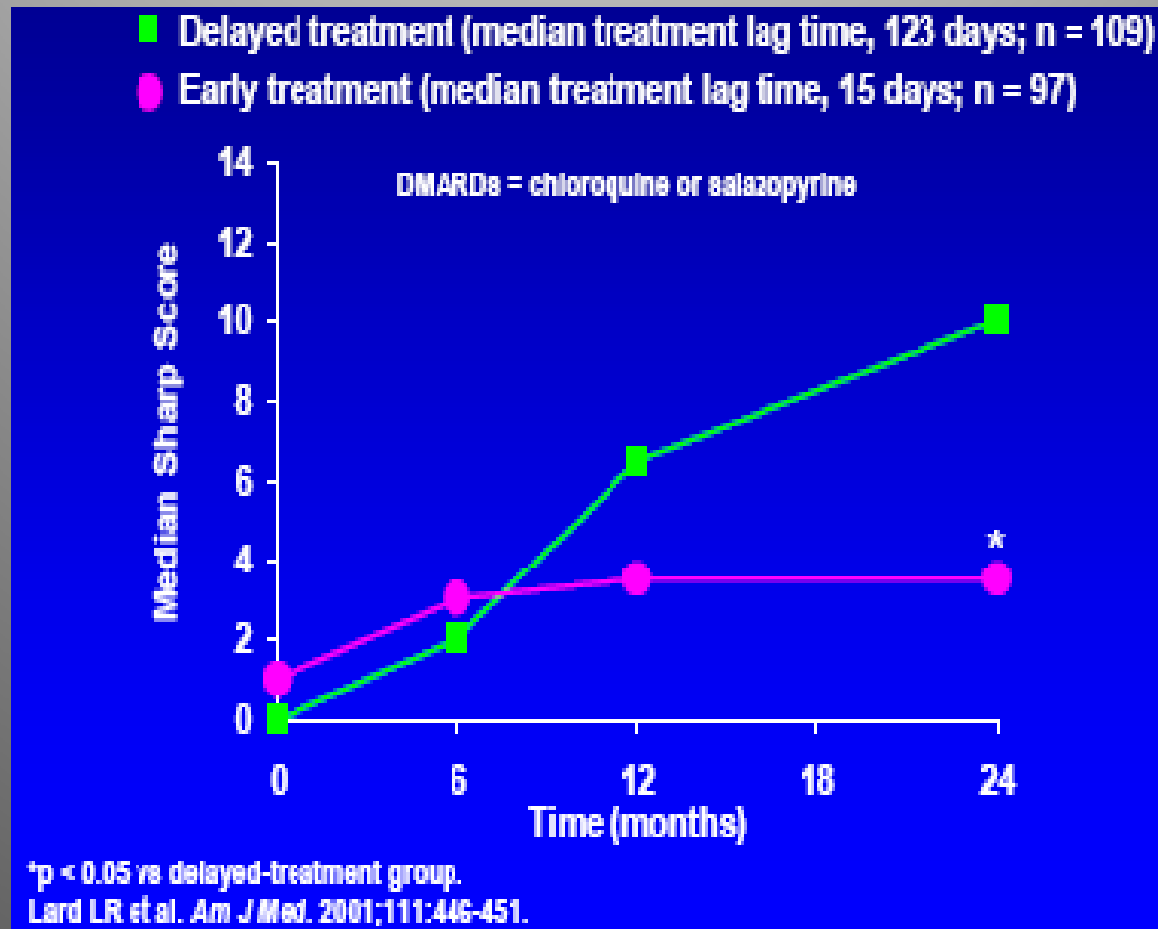
Rate of progression



- Up to 93% of patients with <2 years of RA may have radiographic abnormalities
- Erosions can be detected by MRI within 4 months of RA onset
- Rate of progression is significantly more rapid in the first year than in the second and third years

Fuchs HA et al. *J Rheumatol.* 1989;16:585-591.
McQueen FM et al. *Ann Rheum Dis.* 1998;57:350-356.
van der Heijde DM et al. *J Rheumatol.* 1995;22:1792-1796.

DMARD Treatment: The Earlier the Better



Glucocorticoids

- Local injection: limited to a few joints
- Low-dose oral (<10 mg prednisone):
 - “Bridge-therapy” until DMARD response (polyarticular synovitis)
 - Control of disease despite NSAIDs and adequate trials of DMARDs
 - Loss of independence or employment; flares; special events
 - Toxicity (osteoporosis): dose and duration
- Triamcinolone acetonide (Kenalog): 60 mg IM prn flare

NSAIDS

- Reduce joint pain and swelling
- Improve function

DMARD

Drug	Dosage	Onset of effect	Adverse effects	Monitoring Parameters
Hydroxychloroquine	200-400 mg PO daily	2-6 months	GI upset Retinal toxicity	Fundoscopy every 12 months
Sulfazalazine	2-3 grams daily	1-3 months	GI intolerance Cytopenia Rash Oral ulcers Red urine	CBC every 2- 3 months
Methotrexate	7.5-25 mg PO,SC or IM Weekly + Folic acid 1 mg daily	1-2 months	GI intolerance Rash Cytopenias Oral ulcer Alopecia Hepatitis Pneumonitis Teratogenic	LFT, CBC creatinine monthly x 6 m then every 2-3 months

Table 2. Recommendations for contraindications to starting or resuming therapy with nonbiologic and biologic disease-modifying antirheumatic drugs in RA patients*

Organ system and contraindication	ABA	Anti-TNF α	HCQ	LEF	MTX	MIN	RIT	SSZ
Infectious diseases and pneumonitis								
Acute serious bacterial infection or infection, currently receiving antibiotics	X	X	–	X	X	–	X	–
Upper respiratory tract infection (presumed viral) with fever (>101°F)	X	X	–	–	–	–	X	–
Nonhealed infected skin ulcer	X	X	–	–	–	–	X	–
Latent TB infection prior to initiation of latent TB initiation treatment, or active TB disease prior to completing a standard regimen of anti-TB therapy†	X	X	–	X	X	–	X	–
Active life-threatening fungal infection	X	X	–	X	X	–	X	–
Active herpes-zoster viral infection	X	X	–	X	X	–	X	–
Interstitial pneumonitis (due to RA or unknown cause) or clinically significant pulmonary fibrosis	–	–	–	–	X	–	–	–
Hematologic and oncologic								
White blood cell count <3,000/mm ³ ‡	–	–	–	X	X	–	–	–
Platelet count <50,000/mm ³	–	–	–	X	X	–	–	X
Myelodysplasia	–	–	–	X	X	–	–	–
Treated lymphoproliferative disease of \leq 5 years	–	X	–	X	X	–	–	–
Cardiac								
Moderate to severe heart failure (NYHA III or IV) and left ventricular ejection fraction <50%§	–	X	–	–	–	–	–	–
Liver								
Liver transaminase level 2 times the upper limit of normal	–	–	–	X	X	–	–	X
Acute hepatitis B or C viral infection	X	X	–	X	X	X	X	X
Chronic hepatitis B viral infection, receiving therapy¶								
Child-Pugh class A#	–	–	–	X	X	–	–	–
Child-Pugh class B or C	X	X	–	X	X	X**	X	X**
Chronic hepatitis B viral infection, not receiving therapy								
Child-Pugh class A	–	–	–	X	X	X	–	X
Child-Pugh class B or C	X	X	X**	X	X	X	X	X
Chronic hepatitis C viral infection, receiving therapy								
Child-Pugh class A	–	–	–	X	X	–	–	–
Child-Pugh class B or C	X	X	–	X	X	X**	X	X
Chronic hepatitis C viral infection, not receiving therapy								
Child-Pugh class A	–	–	–	X	X	X	–	–
Child-Pugh class B or C	X	X	X**	X	X	X	X	X
Renal								
Creatinine clearance <30 ml/minute	–	–	–	–	X	–	–	–
Neurologic								
Multiple sclerosis or other demyelinating disorder	–	X	–	–	–	–	–	–
Pregnancy and breastfeeding								
Planning for or current pregnancy	–	–	–	X	X	X	–	–
Breastfeeding	–	–	–	X	X	X	–	–

Drug	Organ system	Contraindication
Hidroxychloroquine	Liver	Chronic Hepatitis B or C not receiving therapy Childs-Pugh class B or C
Sulfazalazine	Hematology Liver	Plts < 50,000 LFT elevation 2-folds the upper limit of normal Acute hepatitis B or C Chronic Hepatitis B or C /Childs-Pugh class B or C
Methotrexate	ID Hematology Liver Pregnancy Breastfeeding	Acute serious bacterial infection Latent TB or active TB Life threatening fungal infection Active HSV infection Interstitial Pneumonitis from RA or unknown cause Clinical significant Pulmonary Fibrosis WBC<3,000 Plts < 50,000 Myelodysplasia Treated lymphoproliferative disease < 5 years LFT elevation 2-folds the upper limit of normal Acute or Chronic hepatitis B or C regardless of Childs-Pugh class Teratogenic Contraindicated

Diagnosed rheumatoid arthritis

In anticipation of possible future biologic therapy:
Check tuberculosis and candida control skin tests
before placing on steroids or other DMARDs.
Baseline chest radiograph

Erosions visible on radiograph?

No

Mild disease

Trial of hydroxychloroquine (Plaquenil), sulfasalazine
(Azulfidine), or minocycline (Minocin)

Adequate control of joint pain and swelling?

No

Yes

Trial of methotrexate,* 10 to 15 mg once per
week ± hydroxychloroquine ± sulfasalazine

Adequate control of joint pain and swelling?

Yes

No

Increase dosage of methotrexate to
20 mg orally once per week; at
25 mg, switch to SC or IM.

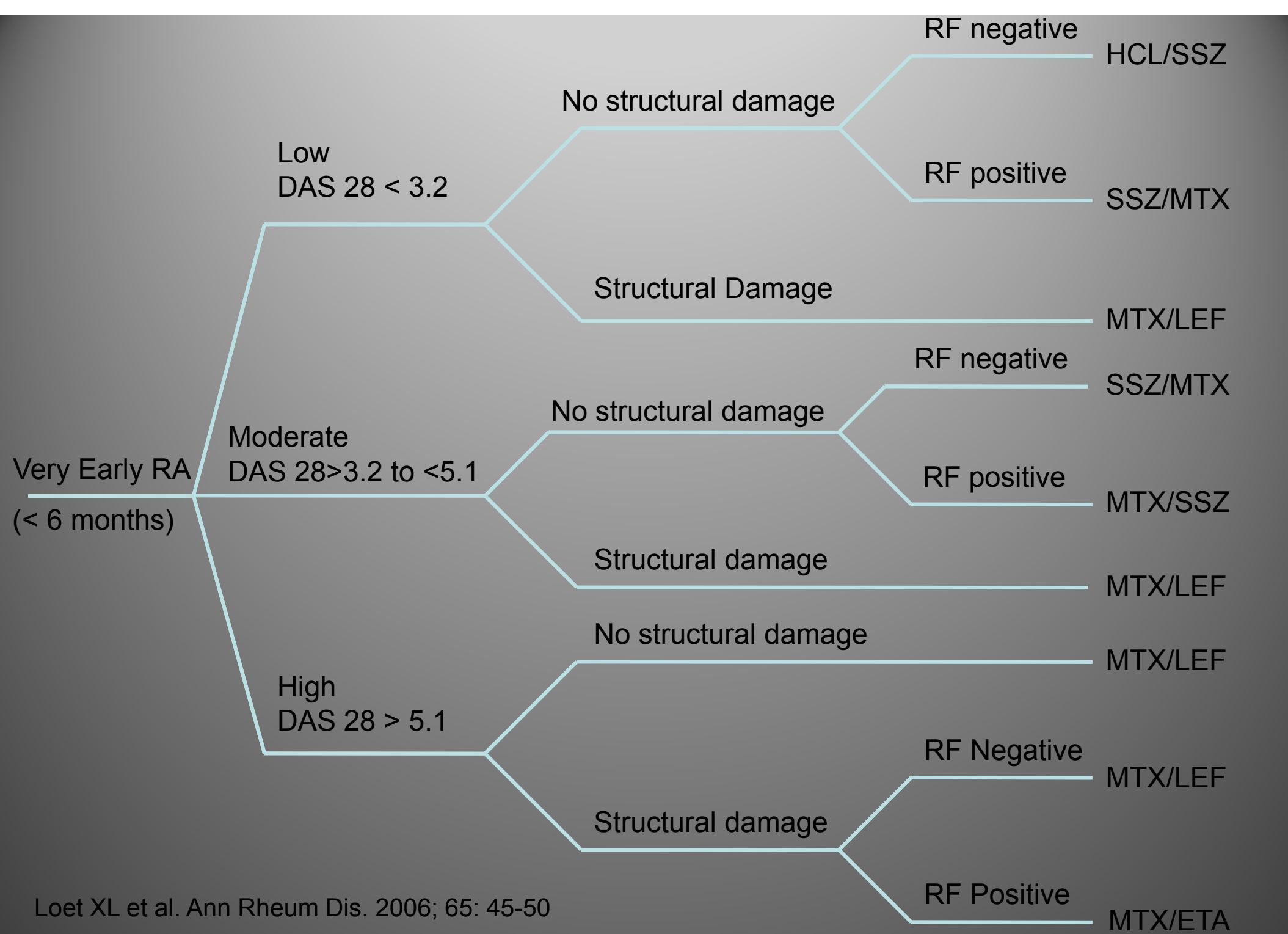
Adequate control of joint pain and swelling?

Yes

No

Monitor disease activity every three to six months.
Annual radiographs

Switch from methotrexate to leflunomide
(Arava) or azathioprine (Imuran);
or add leflunomide or azathioprine to
methotrexate†;
or add a biologic agent to methotrexate.†



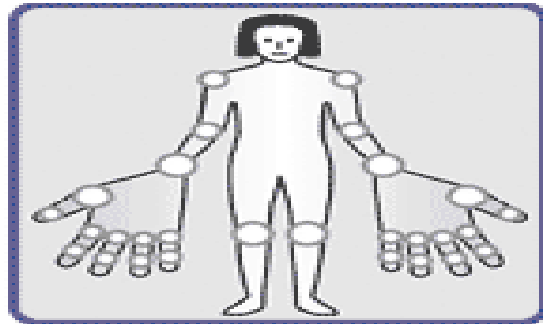
Outcomes Measures

<i>Instrument</i>	<i>Components</i>
DAS	<p>Ritchie index (assess tenderness) Comprehensive swollen joint count (44 joints) ESR Patient global assessment</p> <p>Remission: DAS < 1.6; low disease activity: ≤ 2.4; moderate RA: > 2.4 and ≤ 3.7; and severe RA: > 3.7</p>
DAS28 (http://www.das-score.nl/www.das-score.nl/index.html)	<p>DAS with modifications to include 28-joint count of tender and swollen joints ESR or CRP Patient global assessment</p> <p>Remission: DAS28 < 2.6; low disease activity: ≤ 3.2; moderate RA: > 3.2 and ≤ 5.1; and severe RA: > 5.1</p>

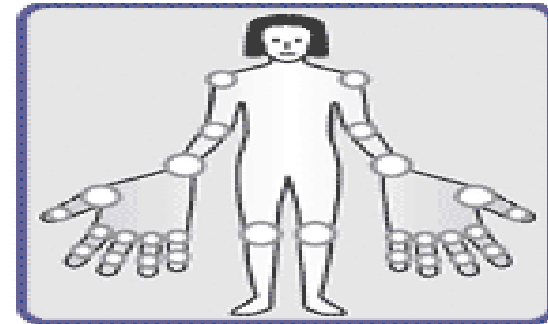
Disease Activity Score (DAS 28)

Joint Status - 28 Joint Count

Tenderness



Swelling



① Joint Count TEN28

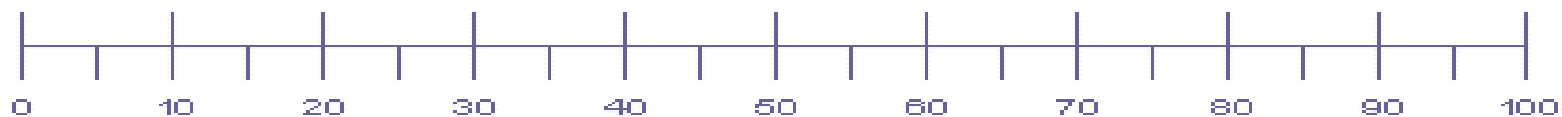
② Joint Count SW28

③ ESR (after 1 hour in mm)

④ **General Health** or patient's global assessment of disease activity
How active has your rheumatoid arthritis been during the last 7 days?*

no activity

highest activity possible



*Please let patient assess this by drawing a vertical line.

Patient's assessment in mm

Formulas for DAS 28 calculation

$$\begin{aligned}
 & 0,56 \times \sqrt{\textcircled{1} \text{ TEN28}} + 0,28 \times \sqrt{\textcircled{2} \text{ SW28}} \\
 & + 0,70 \times \ln(\textcircled{3} \text{ ESR (after 1 hour in mm)}) + 0,014 \times (\textcircled{4} \text{ Patient's assessment in mm}^2) \\
 & = \underline{\quad} + \underline{\quad} \text{ DAS 28}
 \end{aligned}$$

<p>ACR Response Criteria</p>	<p>Improvement (20%, 50%, or 70%) in tender/swollen joint score AND 3 of 5 core set measures: Patient global assessment Physician global assessment Patient pain HAQ Acute-phase reactants (ESR, CRP)</p>
<p>EULAR Response Criteria</p>	<p>3 groups of patients based on DAS/DAS28 response criteria:</p> <p>Good responders Patients with > 1.2 improvement from baseline DAS/DAS28 AND DAS endpoint ≤ 2.4 or DAS28 endpoint ≤ 3.2</p> <p>Moderate responders Patients with > 0.6 but ≤ 1.2 improvement from baseline DAS/DAS28 AND DAS endpoint > 2.4 but ≤ 3.7 or DAS28 endpoint > 3.2 but ≤ 5.1</p> <p>Non responders Patients with ≤ 0.6 improvement from baseline DAS/DAS28 AND DAS endpoint > 3.7 or DAS28 endpoint > 5.1</p>

ACR Criteria for Remission

- Five of the following must be present x 2 months:
 - AM stiffness < 15 min
 - No fatigue
 - No joint pain by hx
 - No joint pain or tenderness on motion
 - No synovitis in joints or tendon sheaths
 - ESR < 30 mm/hr in women; <20 mm/hr in men

MTX is our best anchor drug

	ACR20 12 m	ACR50	ACR70	HAQ
Early RA¹ (ERA)	65%	43%	22%	-0.5
ASPIRE²	54%	32%	21%	-0.68
PREMIER³	63%	46%	28%	-0.80

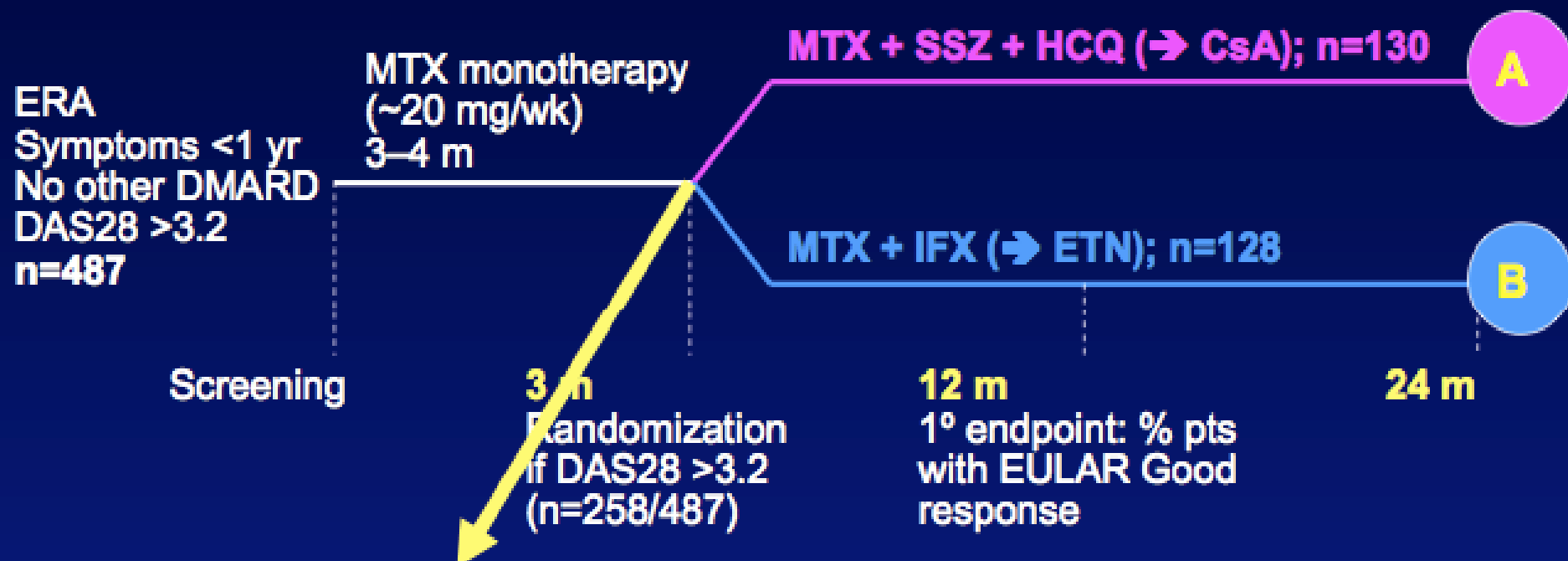
MTX dose 15-20mg/week

1-Genovese MC. *Arthritis Rheum* 2002;46:1443 2-St Clair EW. *Arthritis Rheum* 2004;50:3432 3-Breedveld FC. *Arthritis Rheum* 2006;54:26.

More Studies

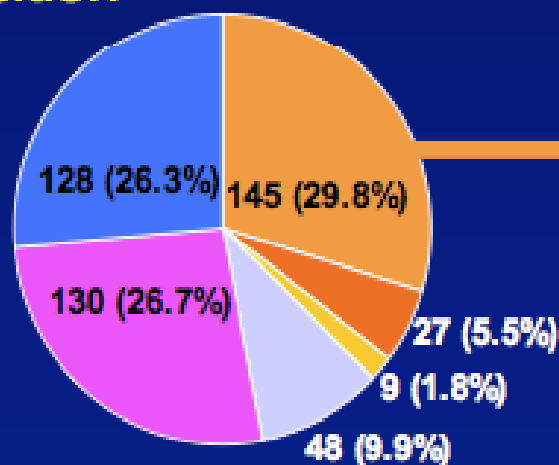
Study (RA Duration)	Interventions	Remission/ Radiographic Outcomes
<p>BeSt (≤ 2 y) 2005 Lasted 1 year</p>	<p>Sequential monotherapy (MTX) Step-up combination therapy (MTX) Combination therapy (MTX, SSZ) + high-dose prednisone Combination therapy (MTX) + infliximab</p>	<p>At 1 y, 32% of all patients had clinical remission ($\text{DAS44} < 1.6$), with no differences between treatment groups At 1 y, significantly more patients in the combination therapy groups (87% and 93%; both $P \leq 0.01$) had no progression of radiographic joint damage than in the step-up (73%) or sequential therapy groups (67%).</p>
<p>COMET (≤ 2 y) 2008 Lasted 1 year</p>	<p>Monotherapy (MTX) Combination therapy (etanercept + MTX)</p>	<p>•At 1 y, significantly more combination therapy than monotherapy patients achieved remission ($\text{DAS28} < 2.6$; 50% vs 28%; $P < 0.001$).</p>

SWEFOT: Triple DMARD vs MTX + anti-TNF



Pt disposition

- MTX responders
- MTX intolerance
- Other disease
- Other
- Arm A
- Arm B



- 30% pts responded to the initial 3–4-month trial of MTX monotherapy (DAS28 <3.2)
- At 12 m, 75% maintained a low disease activity

SWEFOT Trial: Early RA (ERA) Patient - Outcomes in Initial MTX Responders

- N=487 with ERA (symptom duration < 1 year) for SWEFOT trial
- All started MTX with rapid dose escalation to 20 mg/week
- After 3-4 months, 144 patients with DAS28<3.2 continued on MTX & did not enter controlled portion of SWEFOT trial

Patient Outcomes for Initial MTX Responders (n=144)			
Parameter	Time Points		
	6 months	9 months	12 months
DAS28 values (mean ± SEM)	2.4 ±0.09*	2.43 ±0.12*	2.53 ±0.10*
% patients with DAS28 < 3.2	87%*	79%*	75%*
% patients with DAS28 < 2.6	61%*	59%*	60%*

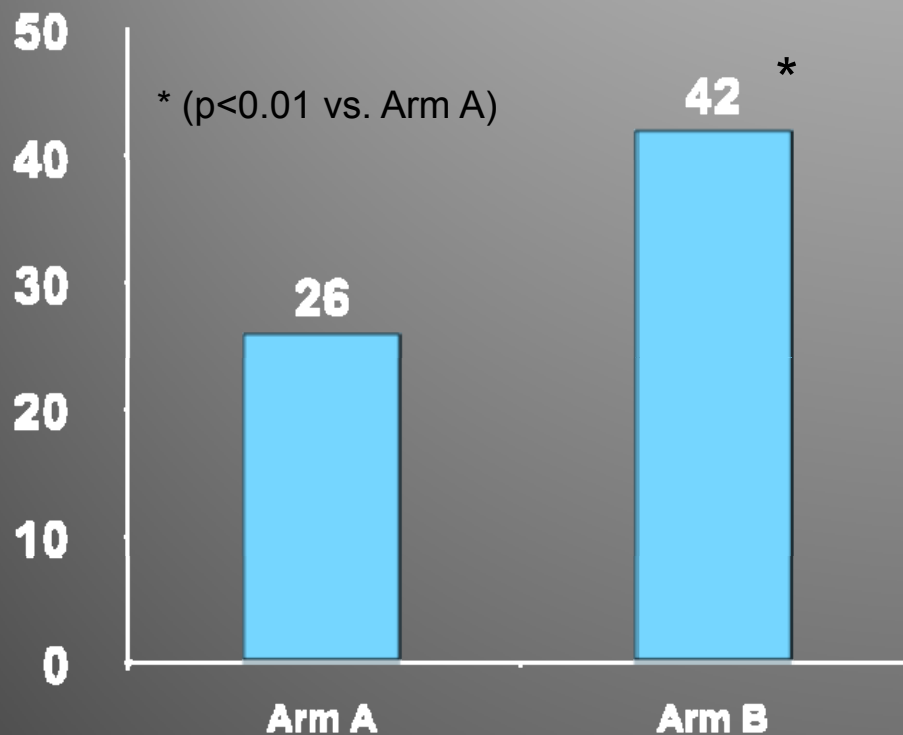
***p<0.001, compared with all other patients in SWEFOT trial analyzed as one group, including those intolerant to MTX**

ERA initial MTX good responders (DAS28<3.2) continue to show very good clinical responses throughout the first year on MTX monotherapy.

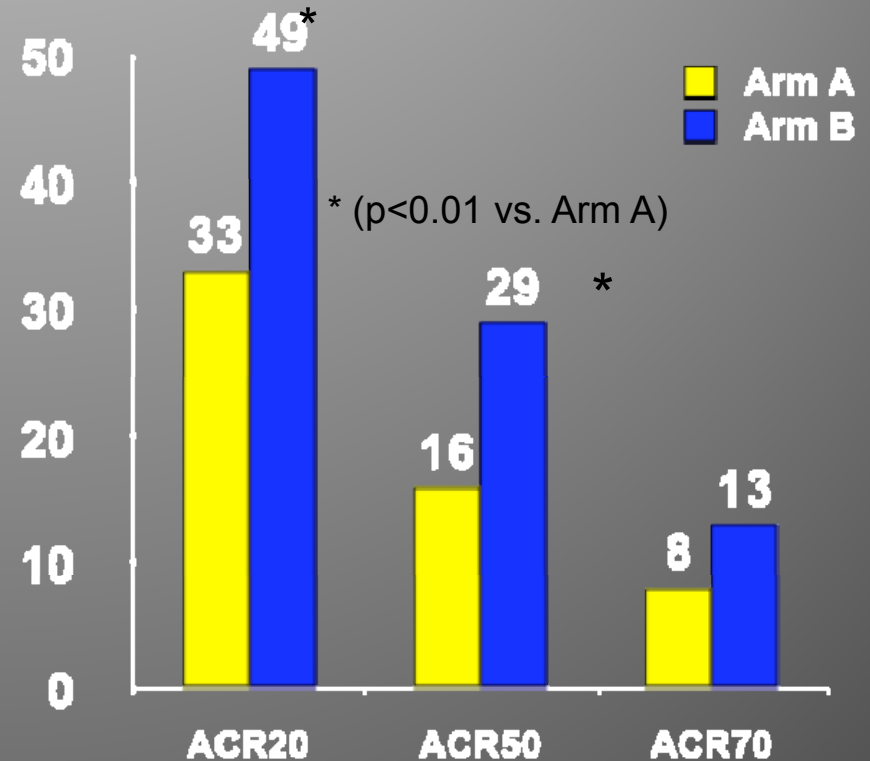
SWEFOT Trial: Addition of DMARDs vs. anti-TNF Therapy in ERA Patients who Failed Initial MTX Therapy

- **Arm A:** Sulfasalazine 1000 mg BID + hydroxychloroquine 400 mg QD (n=130)
- **Arm B:** Infliximab 3 mg/kg/infusion given at 0, 2, 6 weeks, then q 8 wks (n=128)

EULAR Good Response at 12 Months



ACR Responses at 12 Months



Subsequent addition of anti-TNF to reasonable trial of MTX is clinically superior than addition of conventional DMARDs.

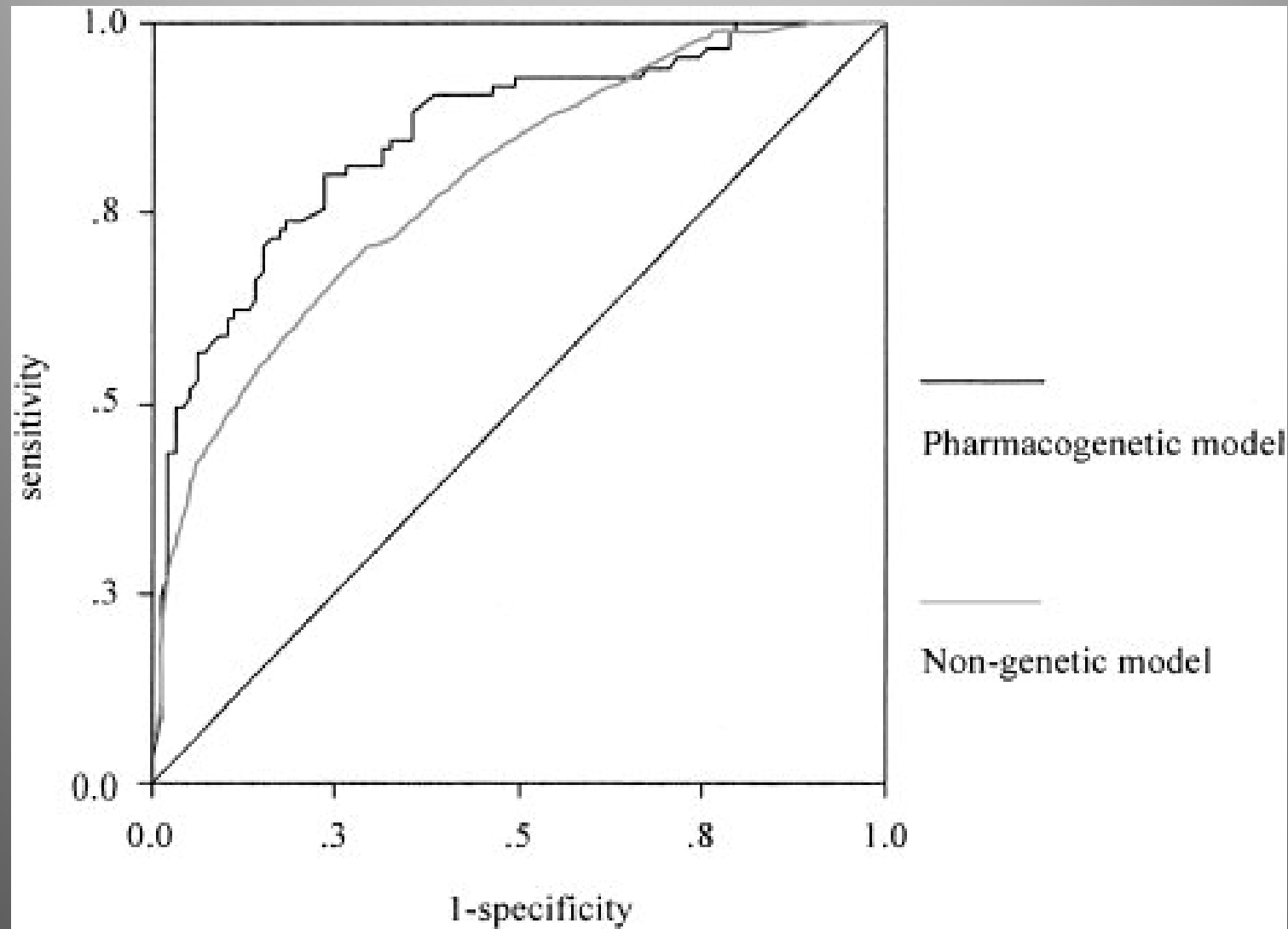
Studies on their way

Study (RA Duration)	Interventions	Remission/ Radiographic Outcomes
TEAR (<5 y) 2009 Lasted 2 years	Init MTX/ETN Init Triple DMARD Step-up MTX/ETN Step-up Triple DMARD	At 6 m, 28% of pt achieved remission on MTX alone. Also at 6m responses were better w/ initial aggressive therapy compared to step up (ACR 20 63 vs 45%). But similar outcomes at 2 years regardless of regimen (no difference in DAS scores)

A Clinic Pharmacogenetic Model to Predict the Efficacy of Methotrexate Monotherapy in Recent Onset Rheumatoid Arthritis

- Non genetic model:
 - Smoking
 - Female
 - Positive RF
 - DAS at baseline
- Pharmacogenetics:
 - Observational variables +
 - Genes related to MTX mechanism of action, purine and pyrimidine synthesis:
 - AMPD1, ATIC, ITPA and MTHFD

Pharmacogenetics



Summary

- Know the clinical and lab findings of RA
- RF is not equal to RA
- Methotrexate is our best anchor drug.
- You can start therapy before referral.
- Moderate to severe RA will likely require biologics.
- Pharmacogenetics could be the answer.

THANK YOU

ANY QUESTIONS?