

Our Approach to the Treat To Target Paradigm in the Management of Patients with Rheumatoid Arthritis: The First Step towards Population Management

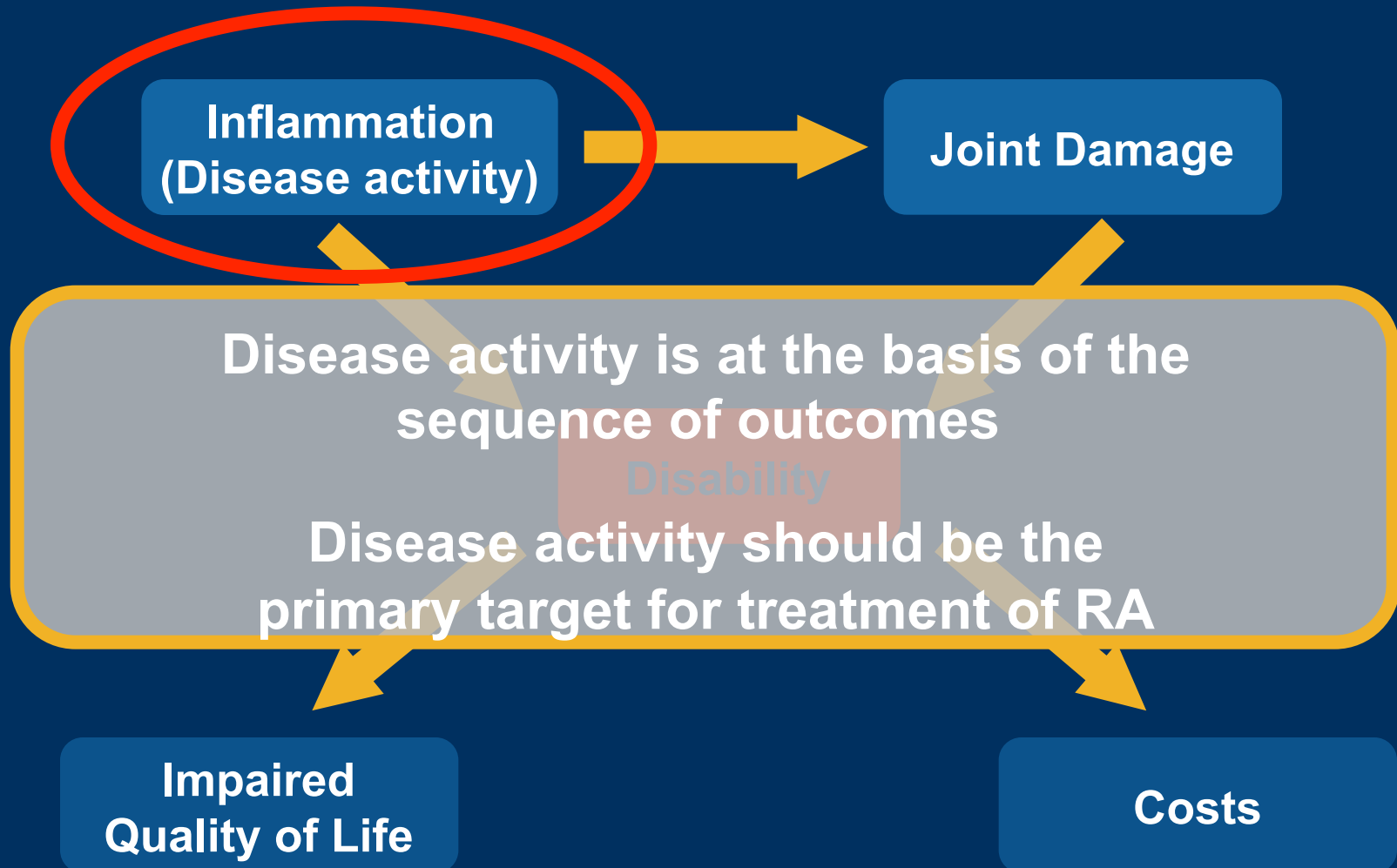
William J. Arnold, M.D. FACP, MACR

Erin L. Arnold, M.D. FACR

Orthopaedics and Rheumatology of the North Shore

August, 2015

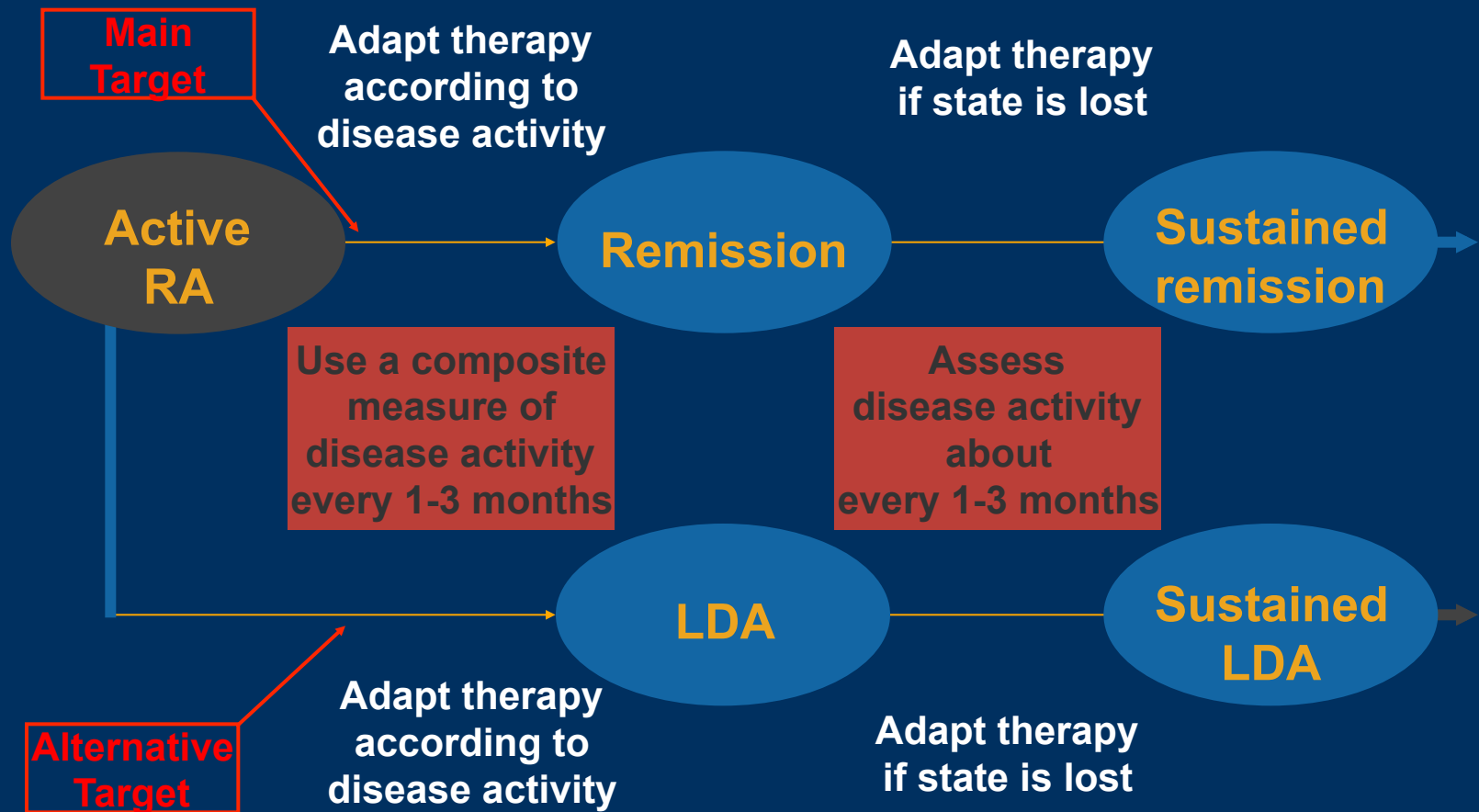
What Is the Target for the Management of RA?



Overall Approach to RA Evaluation and Management

- Early diagnosis-damage can occur early
 - 2010 RA classification criteria
- Measuring RA disease activity
 - Quantitatively establish and document a baseline
 - Compare quantitative RA measurements at progressive time points
- Treatment strategy to continuously strive to push the disease toward improvement, ie low disease activity or remission
 - Advance therapy in stepwise fashion while continuously measuring the disease to achieve goal, or as close as is reasonably feasible.

Treat-to-Target Treatment Algorithm



INFLAMMATORY ARTHRITIS DISEASE ACTIVITY ASSESSMENT FACTS COMPREHENSIVE EVALUATION OF PATIENT'S STATUS

▣ CLINICAL

- MD-HAQ/RAPID-3
- Physician GLOBAL
- SWOLLEN JOINT COUNT



TRUST CLINICAL MEASURES BUT VERIFY WITH LAB AND IMAGING MEASURES

▣ CLINICAL

- MD-HAQ/RAPID-3
- Physician GLOBAL
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COUNT

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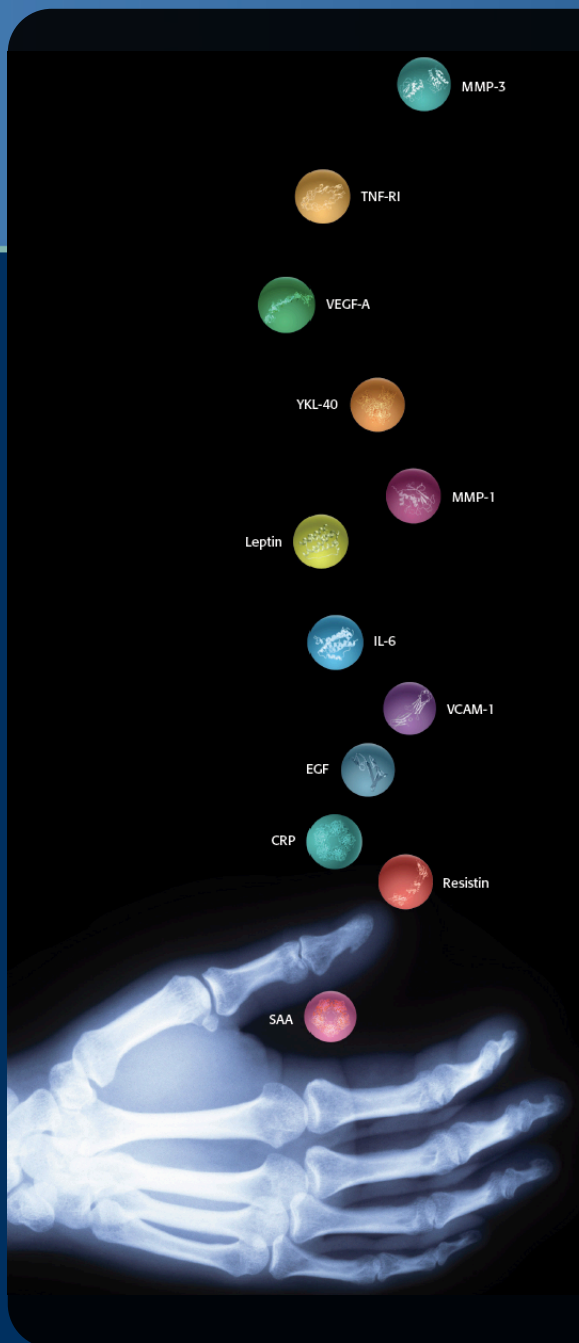
- MD-HAQ/RAPID-3
- Physician GLOBAL
- SWOLLEN JOINT
COUNT

▣ LABORATORY

- ▣ Vectra DA

▣ IMAGING

- ULTRASOUND
PROFILE



Vectra[®] DA:

The multi-biomarker blood test that gives you a deeper look at RA disease activity

Crescendo Bioscience[®] is the sponsor of the presentation.

INFLAMMATORY ARTHRITIS DISEASE ACTIVITY ASSESSMENT FACTS

COMPREHENSIVE EVALUATION OF PATIENT'S STATUS

▣ CLINICAL

- MD-HAQ/RAPID-3
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- SWOLLEN JOINT COUNT

▣ LABORATORY

- ▣ Vectra DA

▣ IMAGING

- ULTRASOUND PROFILE



Objective Measures of RA Disease Activity

- **Vectra DA** is a multibiomarker test with components representing tender and swollen joints and patient global health.
- **Ultrasound** score also contains components associated with tender, swollen joints.
- **Rapid-3** contains info on pain, function and patient global health.

The three measures ,Vectra DA , Rapid-3 and Ultrasound should be complementary in predicting disease severity and managing disease activity to prevent erosions.

Inflammatory Arthritis Ultrasound Profile (IAUP)

- Standardized ,US tech-performed dorsal scan of 4MCPs, 4MTPs, and both wrists/ECUs. Use 16MHz matrix array probe on GE Logic 9. Scans uploaded to cloud for remote analysis.
- Performed as part of clinical visit or by separate appt.
- Score on semi-quantitative scale 0-3 for each component.
- 12 points possible per joint/24 points possible per component/96 total points possible.
- Quantitative measurement of synovial thickness in MCPs and blood flow in Power doppler + tissue.

INFLAMMATORY ARTHRITIS ULTRASOUND PROFILE TM										
Patient Name					Previous IAUP Results					
DOB					Date	PD	ER	EF	SY	Total
Patient #										
Referring MD					MDHAQ Rapid 3: TST:					
Diagnosis					Date	PD	ER	EF	SY	Total
Sonographer										
Date of Scan					MDHAQ Rapid 3: TST:					
Last X-ray: Hand: Foot:										
		Power Doppler (PD)	Erosion (ER)	Effusion (EF)	Synovium (SY)	MCP Synovial Thickness (cm)				
HAND		Gain: _____								
Right						Proximal				
2 MCP						Distal				
3 MCP										
Left										
2 MCP										
3 MCP										
FOOT		Gain: _____				Total(cm)				
Right										
5 MTP										
2 MTP										
Left										
5 MTP										
2 MTP										
TOTAL		24	24	24	24	96				
Scoring System: None 0; Minimal 1; Moderate 2; Severe 3										
Total Synovial Thickness Scores (cm): 0 = < 0.50 1 = 0.50 - 0.59 2 = 0.60 - 0.69 3 = ≥ 0.70										
Impression: _____										
Sonographer Comments: _____										
MDHAQ Rapid 3: _____										
MCP Subtotal 48 MTP Subtotal 48										
WRIST PD EF SY R L ECU PD EF R L										

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Rapid-3 recorded by US tech at same time as IAUP.

Inflammatory Arthritis Ultrasound Profile (IAUP)

Clinical Utilization

Targets to Measure/Follow

- Total points
- Total synovial thickness
 - Normal < 2.0
- Individual component scores
 - Power Doppler Peak Pixel Density
- Signal joint(s) score

Qualitative

Symmetrical v asymmetrical
Relationship to Rapid-3

INFLAMMATORY ARTHRITIS ULTRASOUND PROFILE™										
Patient Name					Previous IAUP Results					
DOB					Date	PD	ER	EF	SY	Total
Patient #					MDHAQ Rapid 3: TST:					
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Right						Proximal		WRIST		
2 MCP						Distal		PD	EF	SY
3 MCP								R		
Left								L		
2 MCP								ECU		
3 MCP								PD	EF	
								R		
								L		
FOOT		Gain: _____				Total(cm)		MCP Subtotal		MTP Subtotal
Right								48		48
5 MTP								MDHAQ Rapid 3:		
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Rapid-3 recorded at same time.

Clinical Utilization

Allows determination of disease severity at onset and improvement/deterioration of individual component or total in response to therapy.

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Inflammatory Arthritis Ultrasound Profile (IAUP)

Clinical Utilization

Frequency of Performing IAUP

Active disease with monthly treatment visits to adjust meds to achieve remission/low disease activity- **Q 3 months**

Sustained low disease activity as measured by SJC, MD global, Rapid-3 and Vectra DA- **Q 6 months**

Sustained Remission as determined by SJC, MD global and Vectra DA- **Q 12 months**.

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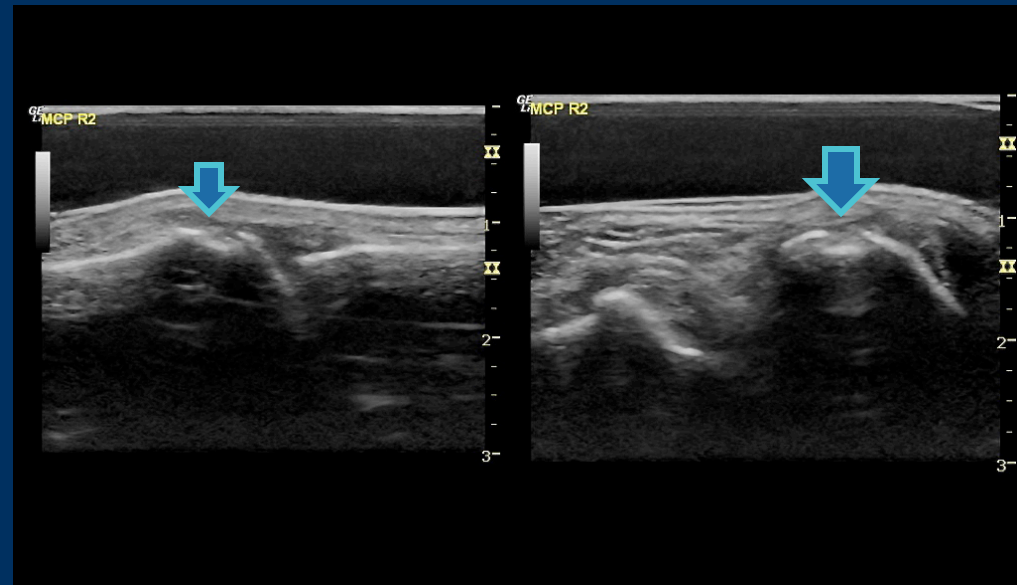
Rapid-3 recorded at same time.

Inter-Grading Scale for Osteoarthritis

Definitions for Bone Erosions, Synovial Fluid, and Synovial Hypertrophy

Bone Erosion

- An intraarticular discontinuity of the bone surface that is visible in 2 perpendicular planes.

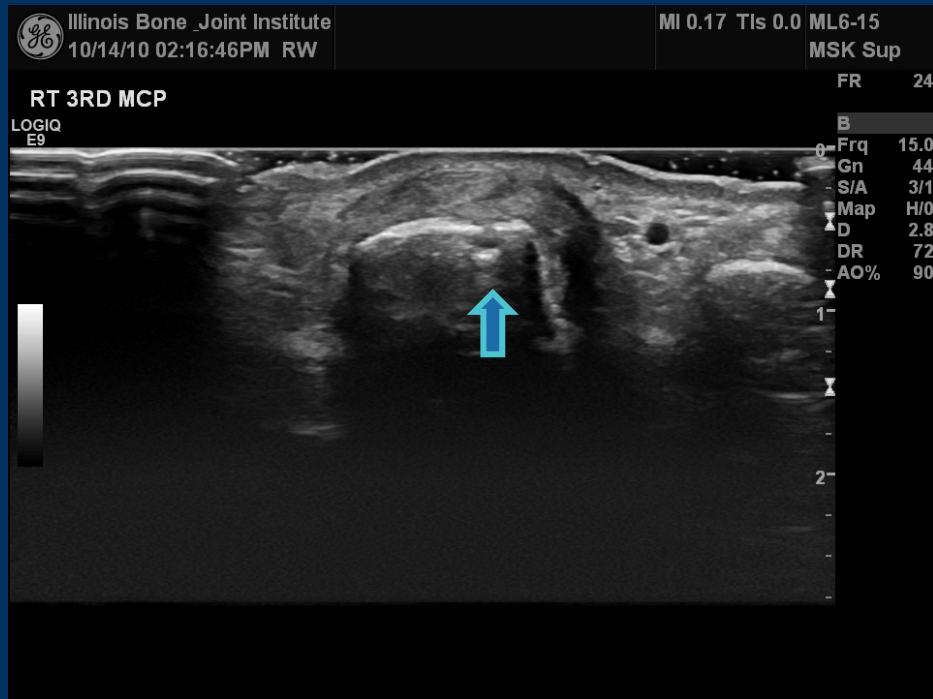


Longitudinal

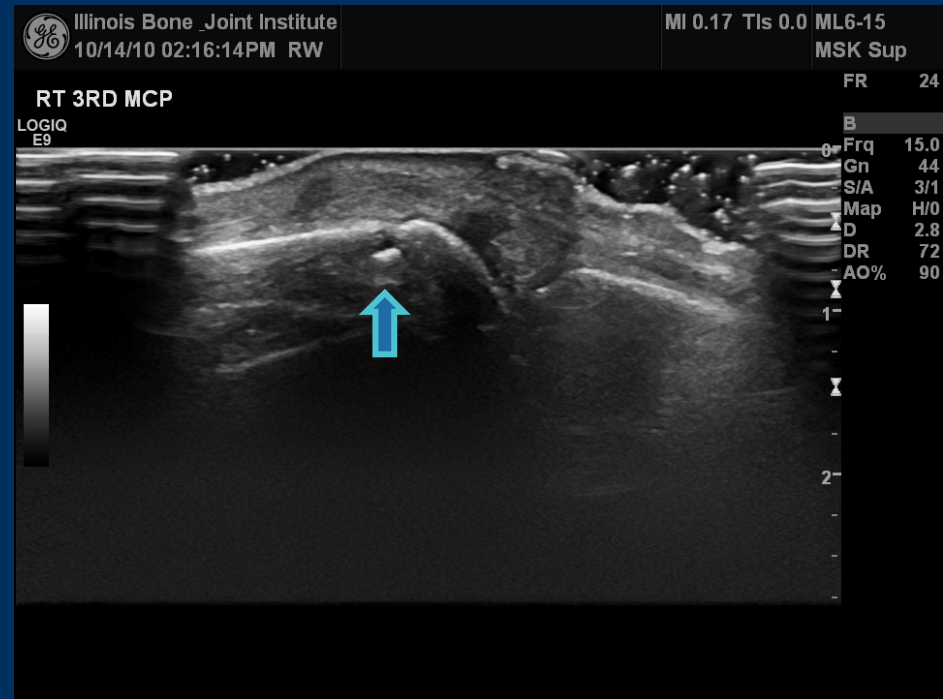
Transverse

Ultrasound Imaging in Rheumatoid Arthritis

3rd MC Head Erosion

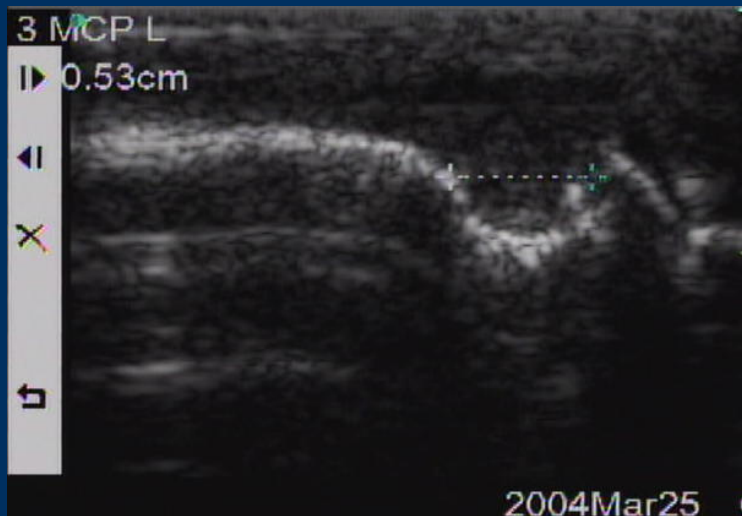


transverse

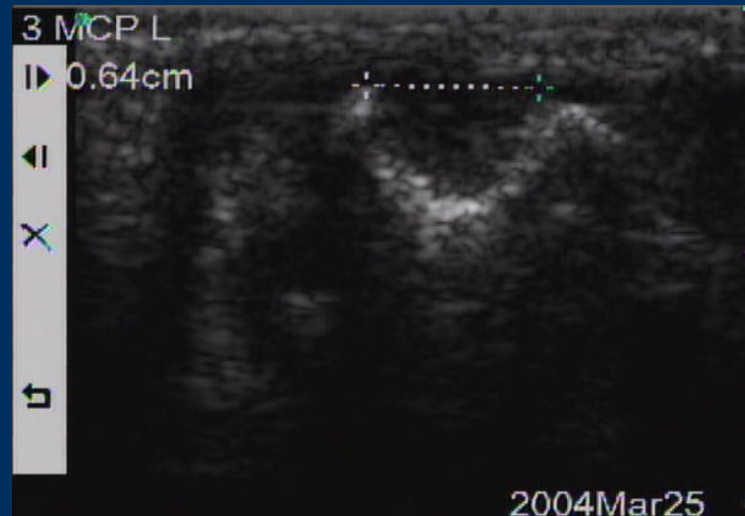


longitudinal

Measurement of Bone Erosion



longitudinal

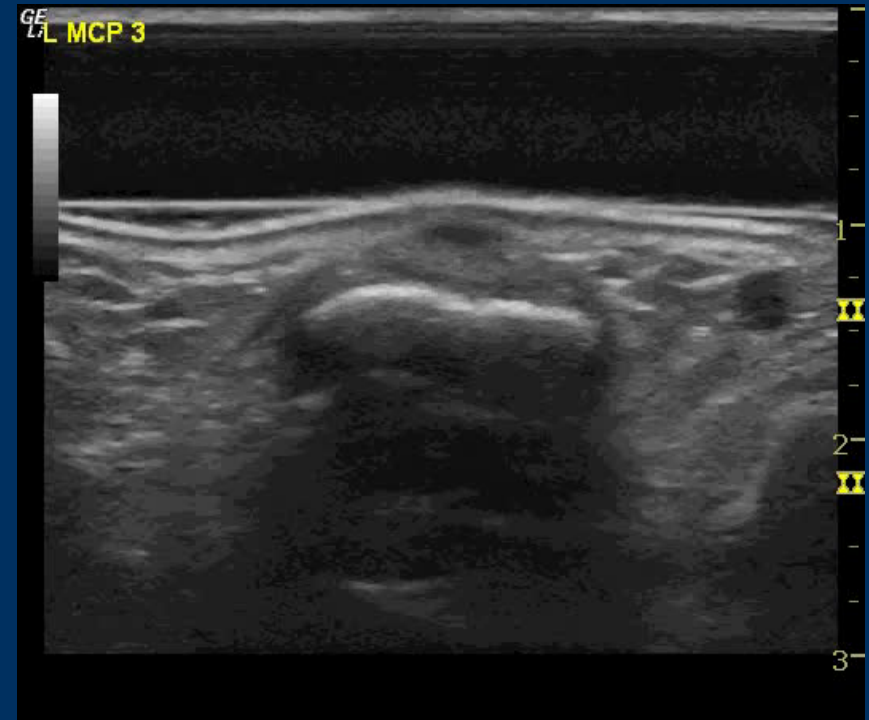
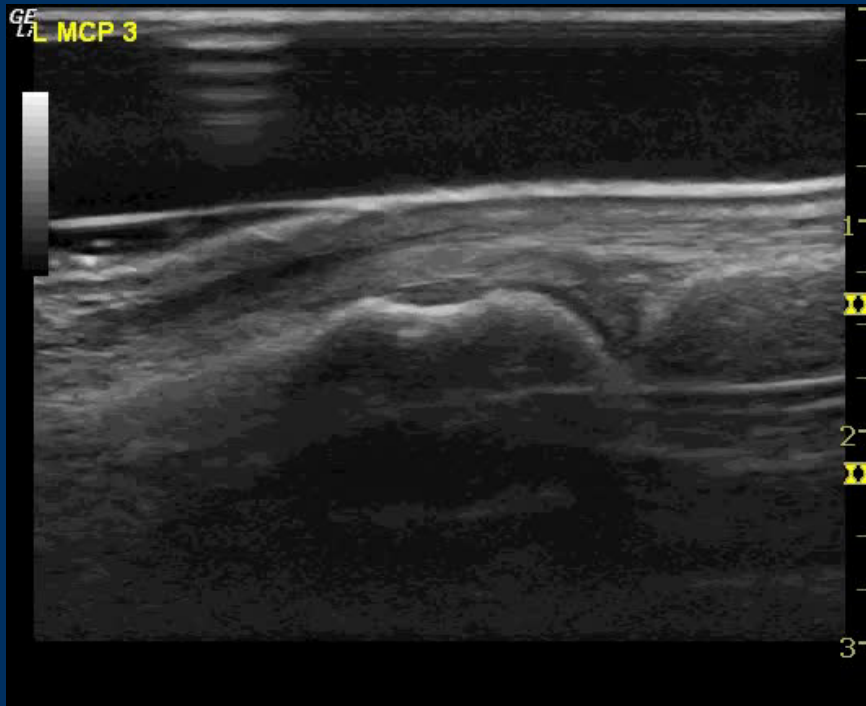


transverse

Ultrasound Imaging in Rheumatoid Arthritis

3rd MC Head Erosion

Dynamic Scanning



Power Doppler

Grade 3

LT 3RD MCP

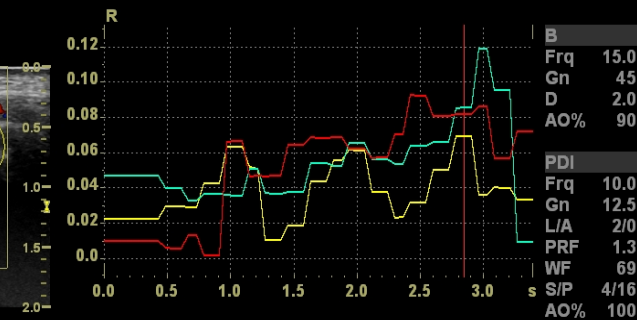
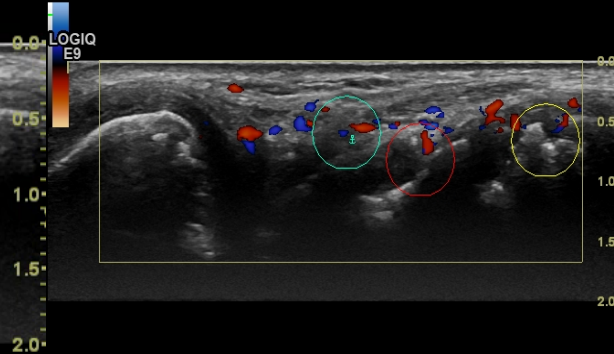
LOGIQ
E9



R Wrist



MI 0.33	TIs 0.7	ML6-15
		MSK Sup



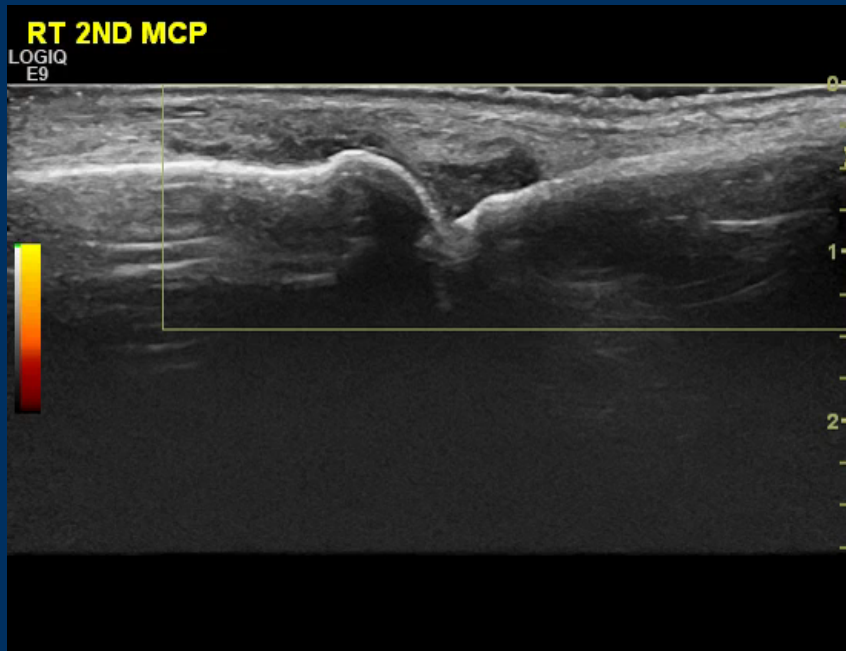
Ratio	Area (mm2)	MaxRatio	Time of MaxRatio	MinRatio	Time of MinRatio
0.070	28.274	0.070	2.844	0.011	1.271
0.086	28.274	0.119	2.965	9.8e-3	3.268
0.082	28.274	0.093	2.421	2.3e-3	0.787



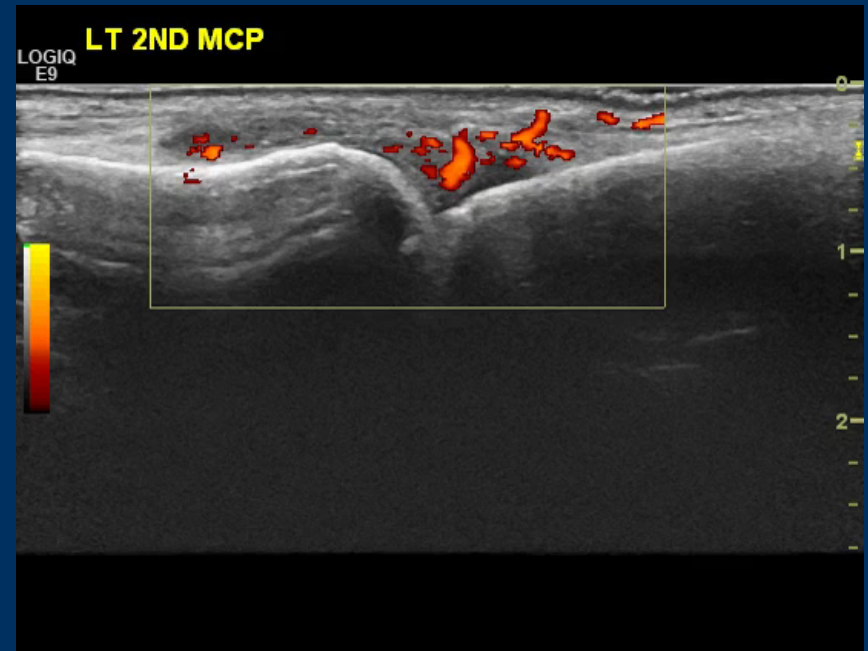
Ultrasound Imaging with Power Doppler in Rheumatoid Arthritis

A TALE OF TWO MCPs

Initial Visit



TST=0.72

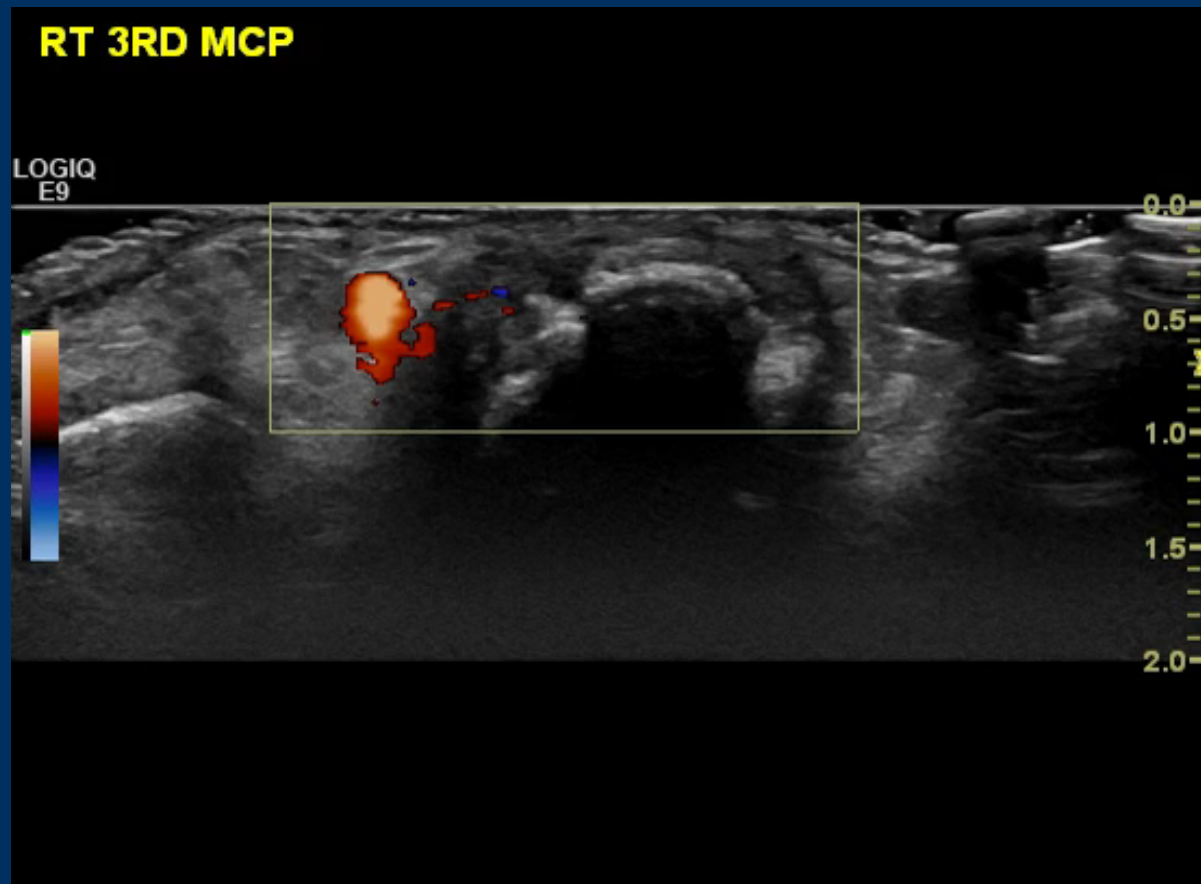


TST=0.70

Measure both grey scale and power doppler as evidence of synovitis
Study both hands and feet not only the dominant side or the most painful

Ultrasound Imaging in Rheumatoid Arthritis

Active (Power Doppler +) Erosion



While erosions can be seen on MRI there is no way to tell if they are active or inactive

Objective Measures of RA Disease Activity

- Provide targets to treat towards
- Facilitate discussions with patients
- Help to select and monitor most efficacious therapies
- Help to decide when/if to taper medications



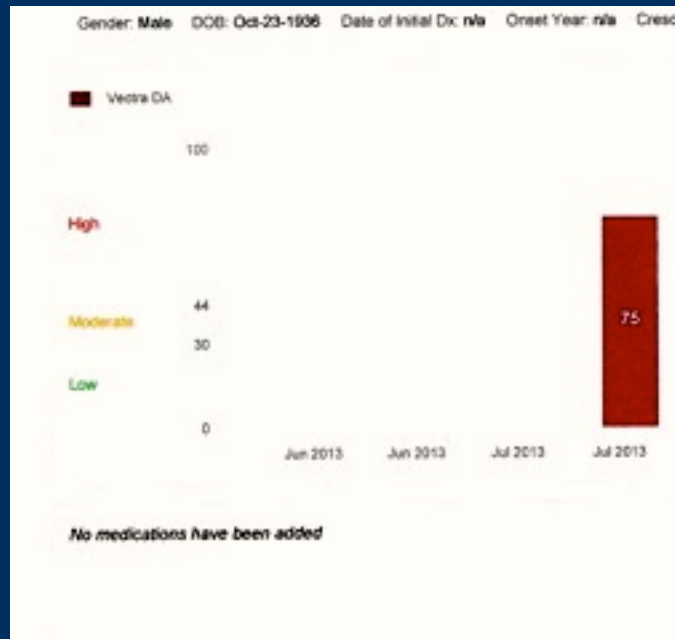
Objective Measures of RA Disease Activity

- **Vectra DA** is a more sensitive measure of RA disease activity than the ESR and CRP.
- Elevated values for Vectra DA highly predictive of development of erosive disease.
- **Ultrasound** is more sensitive than x-ray for the detection of erosions. Erosions are the worst prognostic factor.
- Power doppler positive and grey scale synovitis are highly-predictive of erosive disease.

Objective Measures of RA Disease Activity

High likelihood of erosive disease

Vectra DA= 75



+

Power Doppler = Grade 3



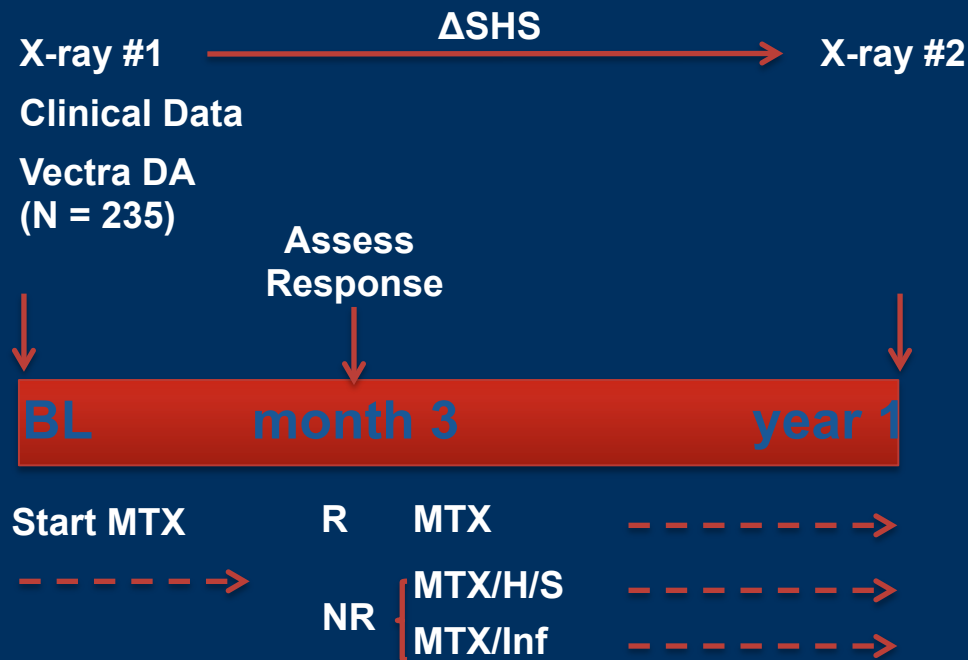
Objective Measures of RA Disease Activity

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SWEFOT Vectra[®] DA Analysis Overview

- Patients from 15 rheumatology units in Sweden
- Early rheumatoid arthritis (eRA) patients with disease duration <1 year, DMARD naïve



R = Responders

NR = Non Responders

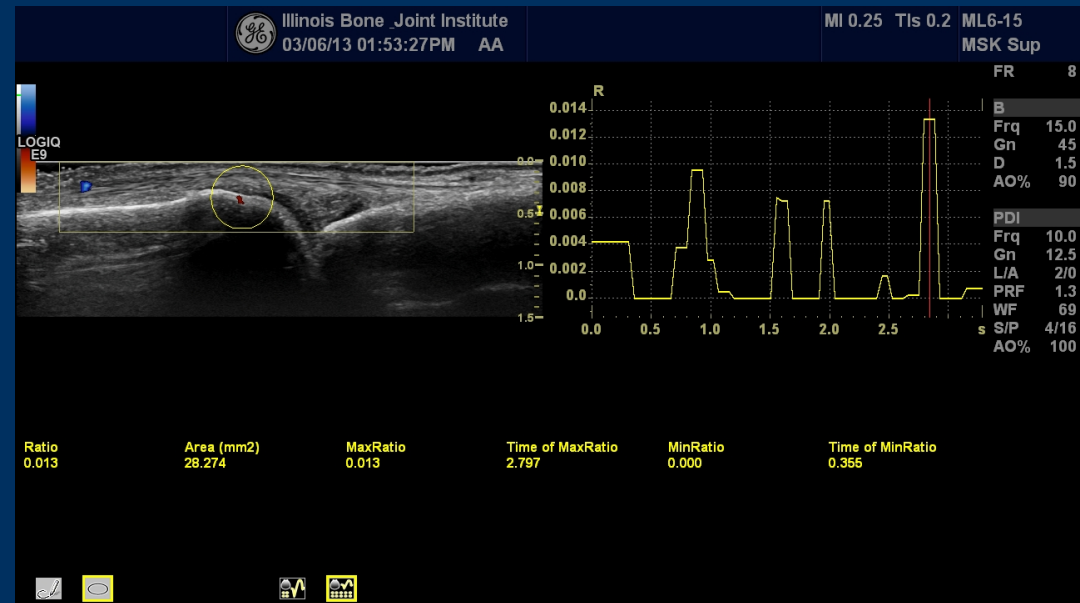
MTX/H/S = Methotrexate with sulfasalazine and hydroxychloroquine

MTX/Inf = Methotrexate with infliximab

Hambardzumyan, K, et al, *Annals of the Rheumatic Diseases* 2014. doi:10.1136/annrheumdis-2013-204986

Objective Measures of RA Disease Activity


- Vectra DA is often elevated prior to the development of erosive disease.
- Early RA - elevated vectra DA with no erosions, +/- PD+ or grey scale synovitis.



Vectra DA= 39;Rapid3=15

Pt AK

Sxs for 2 mos, Rapid 3 =15.3, SJC=0
RF/CCP strong+, +Family Hx

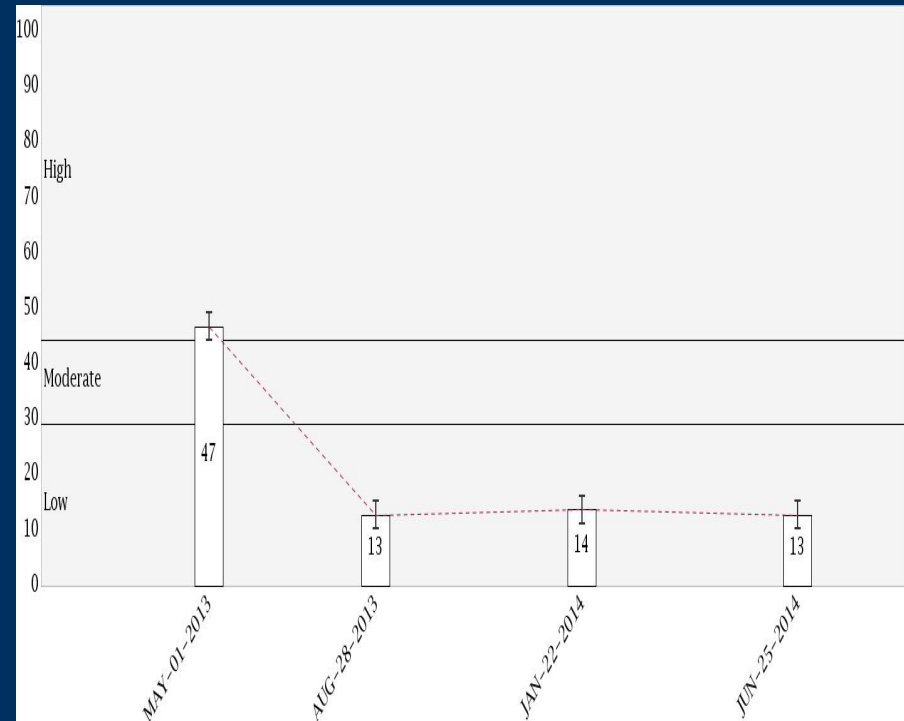


Illinois Bone Joint Institute

05/07/13 05:37:27PM AA

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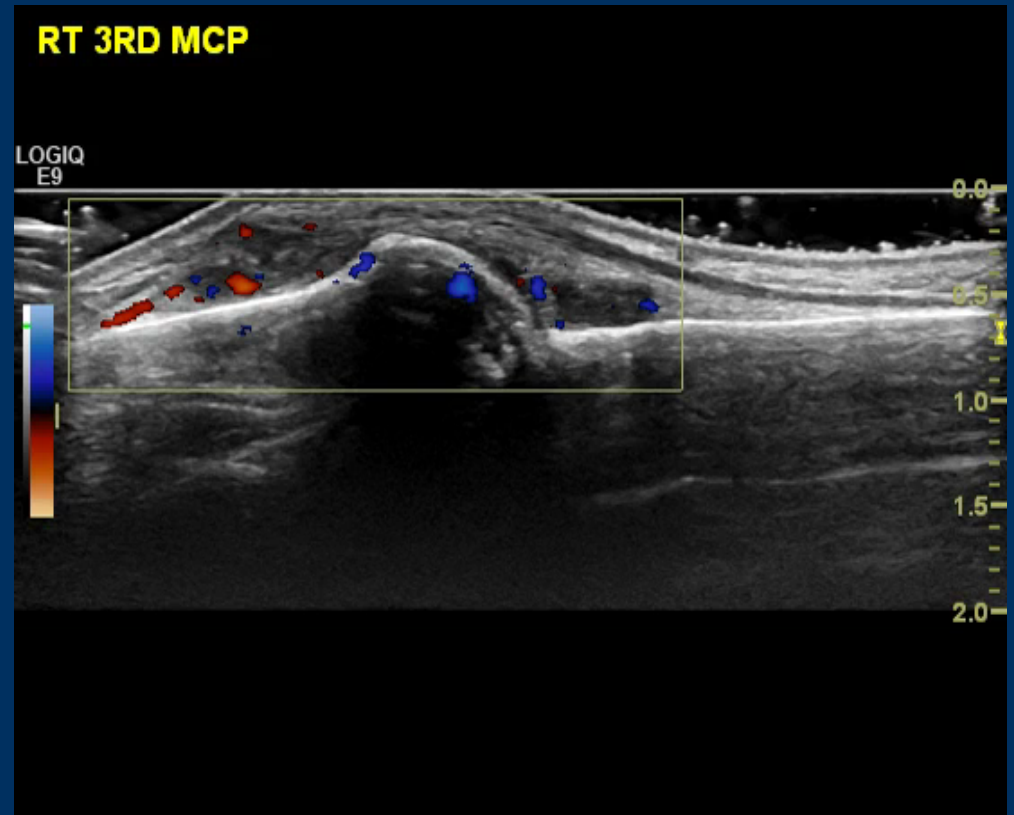
Parameter	Value	m1	m2	m3	m4	m5	m6	Method
Examiner's Comments								
	PD ER EF SY	MCP 5/48		MTP 0/48				
R2MCP	0 0 0 1	GAIN 12.5		12.5				
R3MCP	0 0 0 1	TST 2.09						
L2MCP	0 0 1 1	RAPID 3: 15.3						
L3MCP	0 0 0 1	BLT ECU PD 0, EF 0						
R5MTP	0 0 0 0	LT ECU DISPLACED						
R2MTP	0 0 0 0							
L5MTP	0 0 0 0							
L2MTP	0 0 0 0							
TOTAL	0 0 1 4	5/96						



Begin Mtx tabs 20 mg weekly on 5/14
Rapid3= 4 on 8/28

Objective Measures of RA Disease Activity

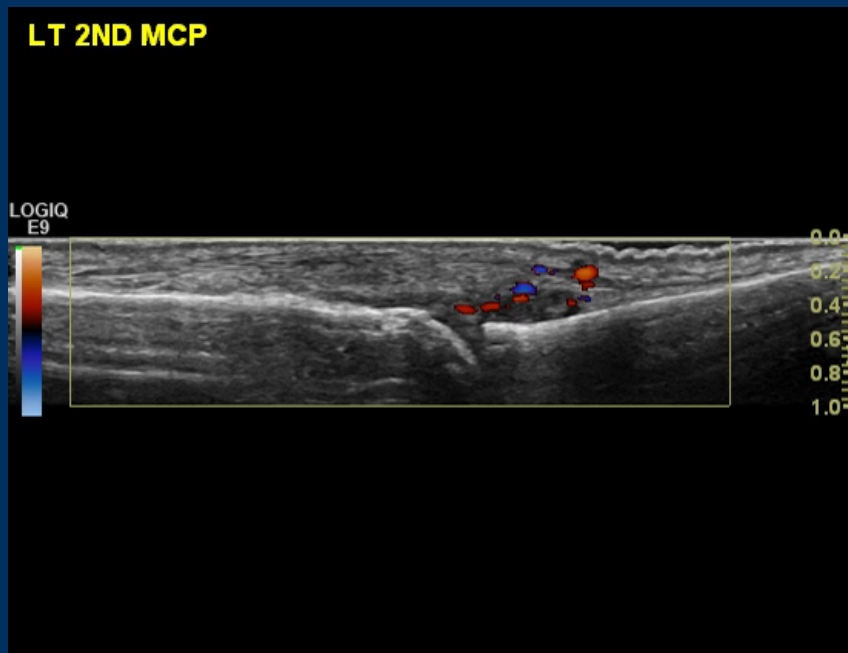
- Ultrasound has defined a new type of erosion...the active erosion.
- Manifest as a power doppler + erosion



While erosions may not heal....a target of treatment is to change an active erosion to an inactive erosion.

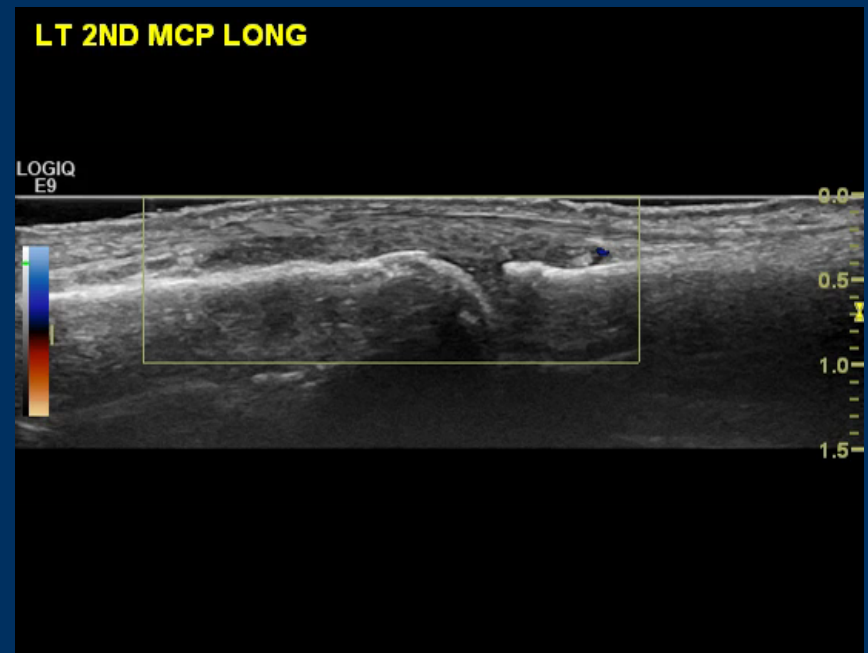
Pt CN

August, 2011



scMtx 25 mg/wk

August 2012



**Sc Mtx 25 mg/wk
Enbrel 50 mg/wk**

Objective Measures of RA Disease Activity

- Provide targets to treat towards
- Facilitate discussions with patients
- Help to select and monitor most efficacious therapies
- Help to decide when/if to taper medications



Pt CM
RF/CCP strong +
>10 yr Hx of active disease

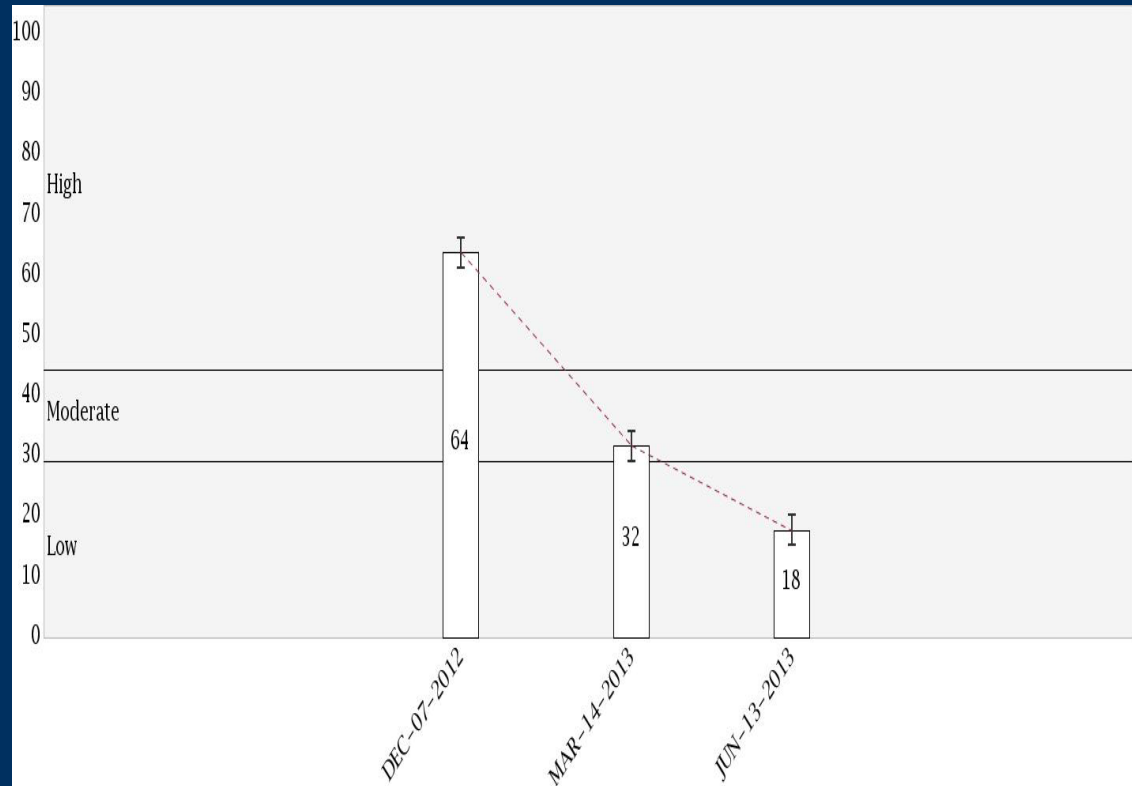
Pt resisted therapy while caring for his wife with RA of even longer duration.

She passed from complications of therapy.

Pt was begun on Mtx 4/12 with definite benefit but persistent pain.

Qgold + for Tb so required treatment before anti-tnf.

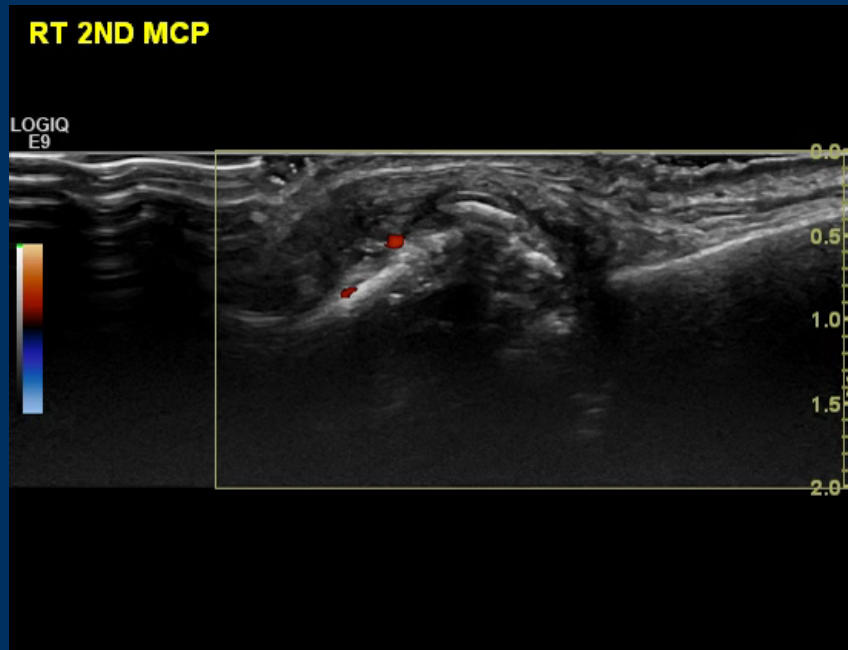
12/7 added Cimzia



**RF/CCP strong +
>10 yr Hx of active disease
Treatment of active erosion**

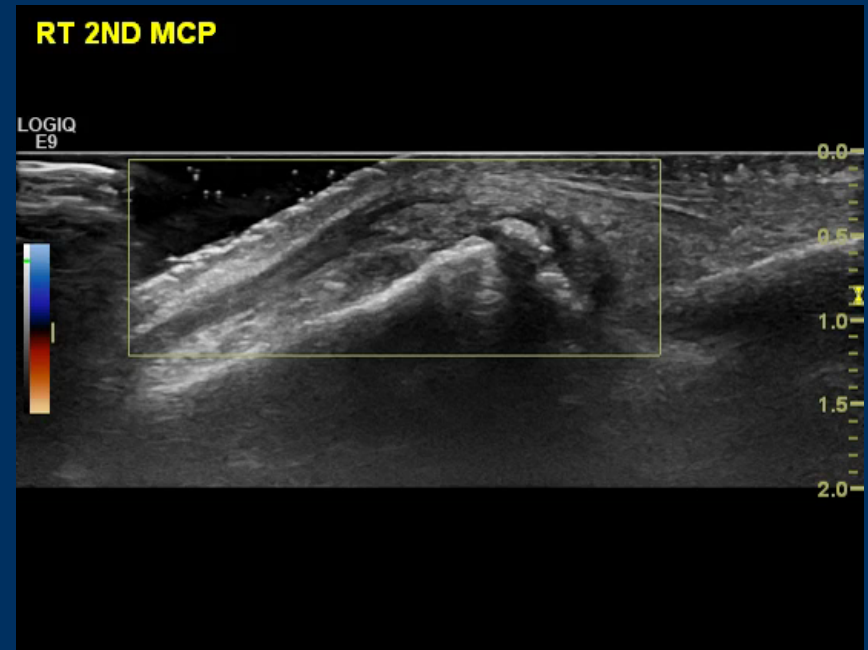
10 27 2012

Vectra DA = 64



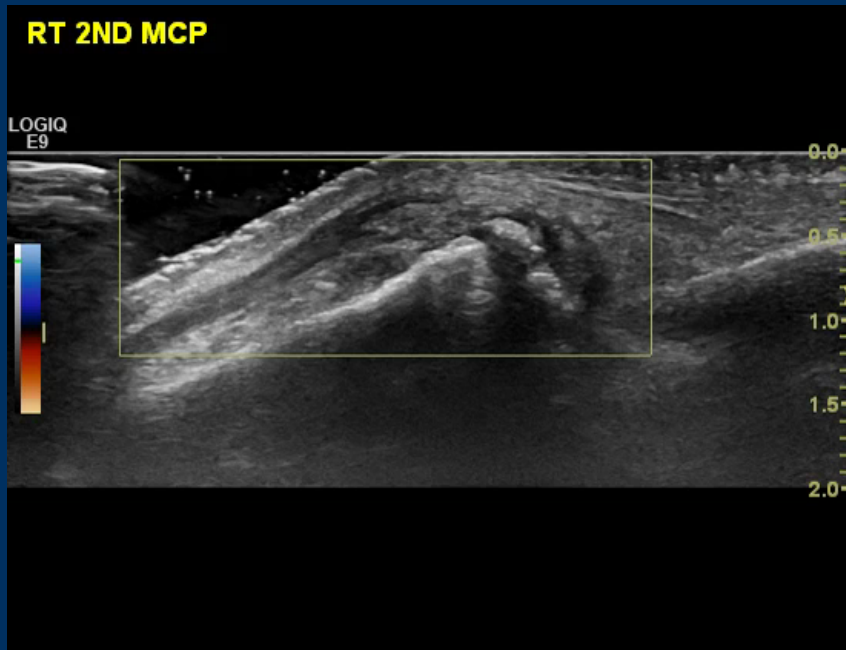
3 14 2013

Vectra DA = 32

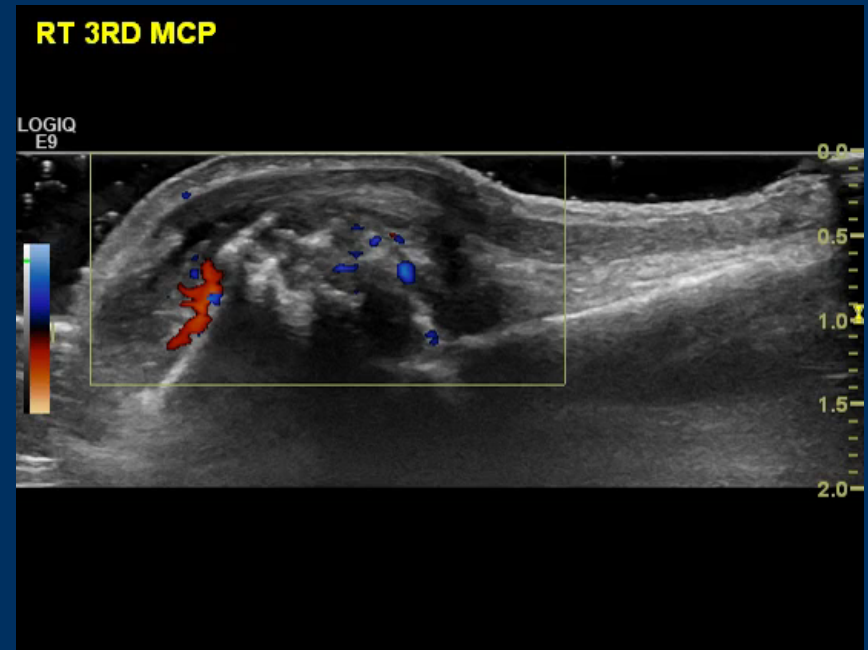


**RF/CCP strong +
>10 yr Hx of active disease
Treatment of active erosion**

**3 14 2013
Vectra DA = 32**



**3 14 2013
Vectra DA = 32**



While the R 2nd mcp is now PD-, the 3rd mcp is +, also with moderate Vectra DA. Pt's Mtx increased to 25 mg weekly. 4 months later Rt 3rd mcp was PD- and Vectra DA= 28.

Summary

- For patients with RA, it is possible and desirable to objectively measure disease activity from multiple aspects and treat to target.
- Patient preference will largely dictate treatment progression but this can be influenced by objective data.
- Vectra DA, a multiple component bioassay, offers a **biologic measure** of RA disease activity.
- An Ultrasound profile of important components of RA inflammation and joint destruction offers an **imaging measure** of RA disease activity and severity.

Conclusion

- No one, single measure will suffice to fully describe disease activity in patients with RA.
- A Synthesis of clinical measures of patient and physician assessments of disease activity complemented by laboratory and imaging measurements will be necessary to give the full picture of disease activity and severity.
- Future treatment decisions based on this synthesis of objective measures will give the best outcomes over time for patients with RA.

NEXT STEPS

Population Management for Rheumatoid Arthritis

- Enroll all RA patients into OUR registry cataloguing objective measures, ie IAUP, Vectra DA, Rapid-3, Physician global, swollen joint count.
- Stratify patients as high, medium or low disease activity.
- Focus initially on the timely assessment of high disease activity patients (minimum Q 3 months).
- Re-design practice workflow, including pre-visit assessment.

Our Approach to the Treat-to-Target Paradigm in the Management of Patients with Rheumatoid Arthritis: The First Step towards Population Management

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