

EARLY RHEUMATOID ARTHRITIS

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- الف: بر اساس Expert Opinion نامبرده مبتلا به RA بوده و خانم ۵۳ ساله ای بعثت ارترازی از دو ماه قبل مراجعه کرده است. تجویز منیمایم MTX احساس خستگی و خشکی صبحگاهی در حد ۱۵ دقیقه دارد. سابقه بیماری دیگری مثل پسوریازیس ندارد. در معاینه تورم مفصلی و تپش مفاصل مزاحله پرو کلینیکال تویجوزو تحت نظر Anti ccp و RF که با تیر ۵ برابر نرمال است، سایر آزمایشات از قبیل Ca,P, ESR,CRP,TSH ANA. ج: بر اساس نمرات 2010 ACR/EULAR و افزایش ضخامت نسبی سینوویوم دریافتی MTX می باشد (حدود ۵ مفصل) PIP دستها دارد. کدامیک به نظر شما نزدیک تر است؟
- د: بیمار در مرحله Very Early RA بوده و تجویز HCQ مانع پیشرفت بیماری میشود

■ Definitions

■ Importance

■ Diagnosis

■ Predictive response biomarkers

Historical aspect of RA

1980s approach

- RA is a benign disease and joints joint damage and disability occurring slowly and late
- Emphasizing on treating symptoms
- NSAIDs considered least toxic
- MTX and GCs considered most toxic
- DMARDs were only initiated when patients had demonstrable radiological damage

Quinn, *Clin Exp Rheumatol* 2003; 21 (Suppl. 31):S154-S157. ⁴

1990s approach

- Joint damage occur in early course of RA
- Disease duration was of foremost importance in predicting response to DMARD therapy.
- Early treatment, better outcome

DEFINITIONS

- THE CHANGING DEFINITION OF EARLY DISEASE
- A wide range of definitions have been used
- In the past, studies used a cut-off of less than 5-7 years from the time of **diagnosis** to define early disease
- By the 1990s, diagnosis within 12 to 24 months was considered early, with definitions now based on time from **symptom onset**

2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

- Early RA : duration of disease/symptoms of less than 6 months, where “duration” denotes the length of time the patient has had symptoms/disease, **not the length of time since RA diagnosis**
- Established RA: duration of disease/symptoms of ≥ 6 months or meeting 1987 ACR RA classification criteria

Singh. et al. Arthritis & Rheumatology. 2016 Jan;68(1):1-26.

- **Very early RA:** symptom duration less than 3 month
- A plethora of terms currently used to describe individuals in disease phases before the fulfillment of classification criteria for RA, including 'early RA', 'very early RA' and 'pre-RA'
- **Preclinical RA:** the presence of RA-related autoimmunity in absence of clinically apparent inflammatory arthritis

EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis

Danielle M Gerlag,¹ Karim Raza,² Lisa G M van Baarsen,¹ Elisabeth Brouwer,³

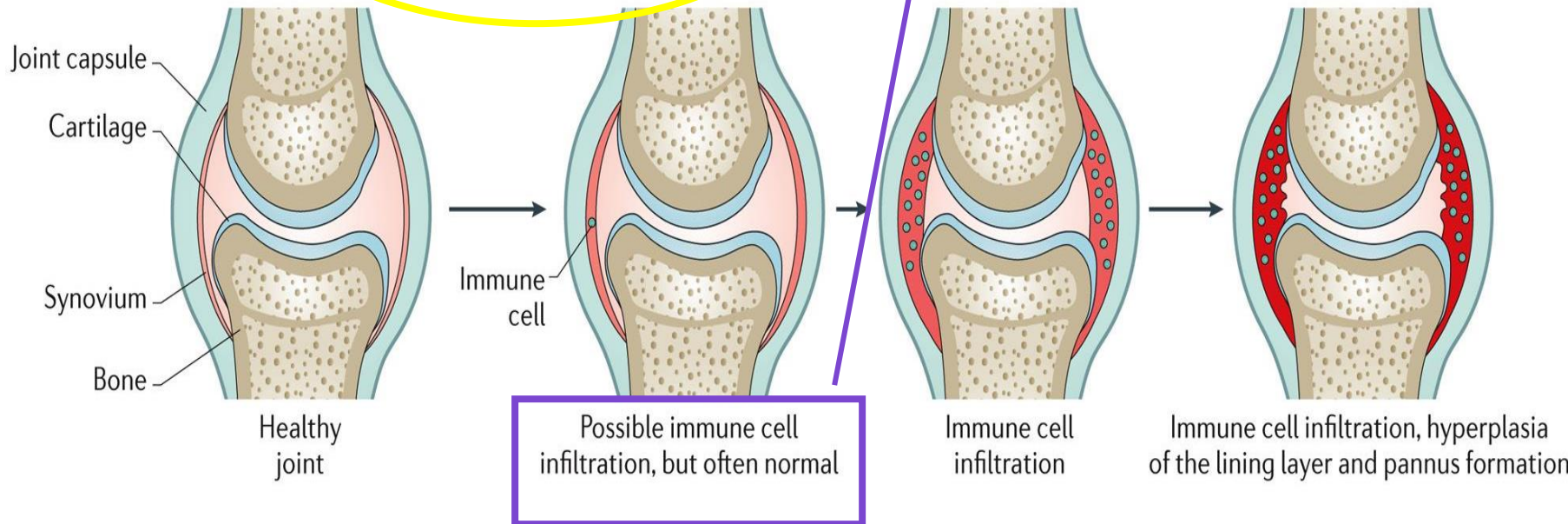
No symptoms or signs of autoimmunity

Asymptomatic autoimmunity
Increased levels of cytokines, chemokines and CRP in the circulation

Early symptomatic autoimmunity

Undifferentiated arthritis

Classifiable RA



- Definitions
- Importance
- Diagnosis
- Predictive response to treatment

Importance of early RA

An opportunity to prevention?

OR

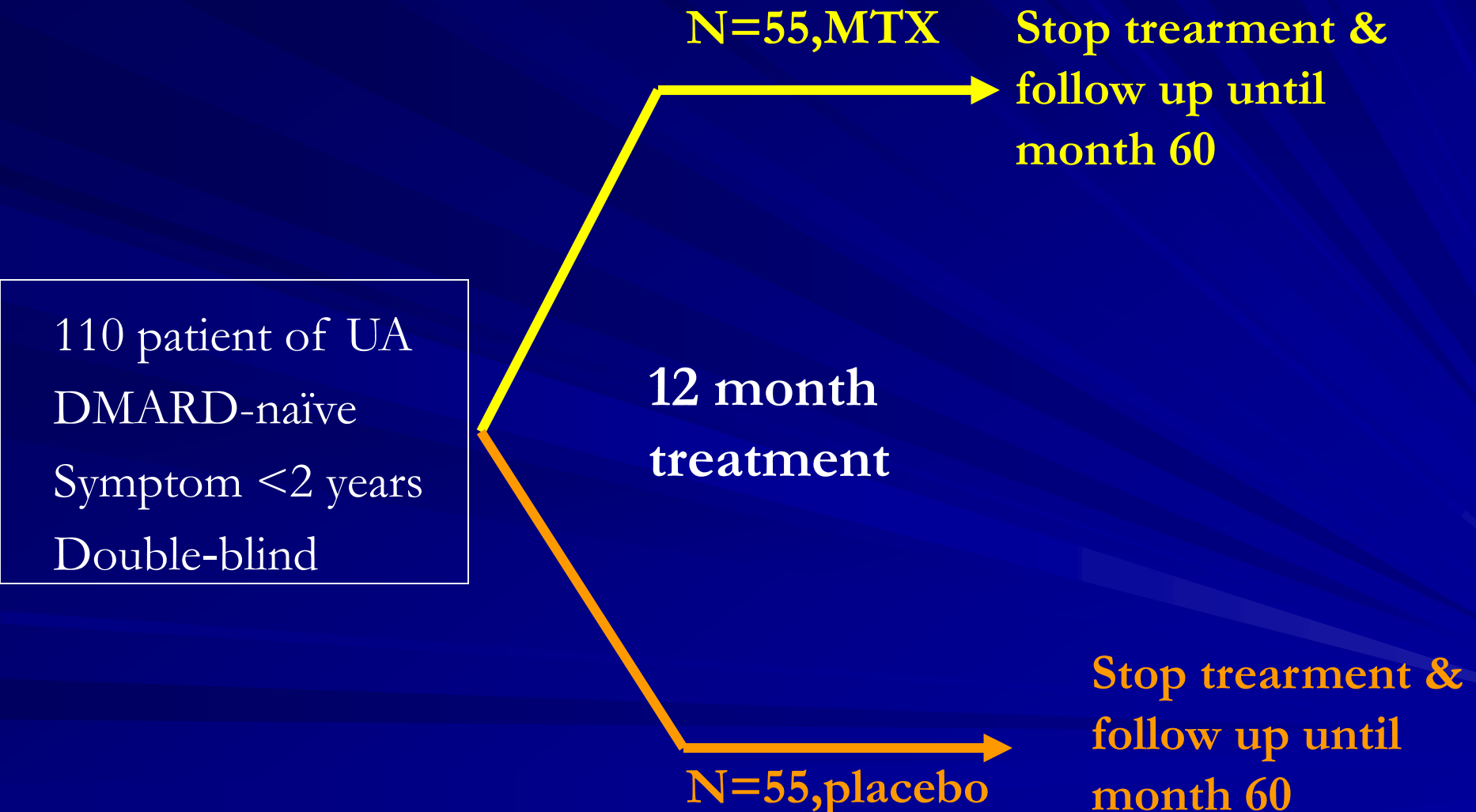
An opportunity to better outcome?

Does the use of tumour necrosis factor antagonist therapy in poor prognosis, undifferentiated arthritis prevent progression to rheumatoid arthritis?

B Saleem, S Mackie, M Quinn, S Nizam, E Hensor, S Jarrett, P G Conaghan, P Emery

- Patients with UA of less than 12 months duration
- Double-blind, placebo controlled trial of infliximab or placebo monotherapy administered at weeks 0, 2, 6 and 14
- By week 52, 100% patients in the infliximab group and 71% patients in the placebo group had developed RA

The **PRO**bable rheumatoid arthritis: **M**ethotrexate versus **P**lacebo **T**reatment (**PROMPT**):



PROMT trial

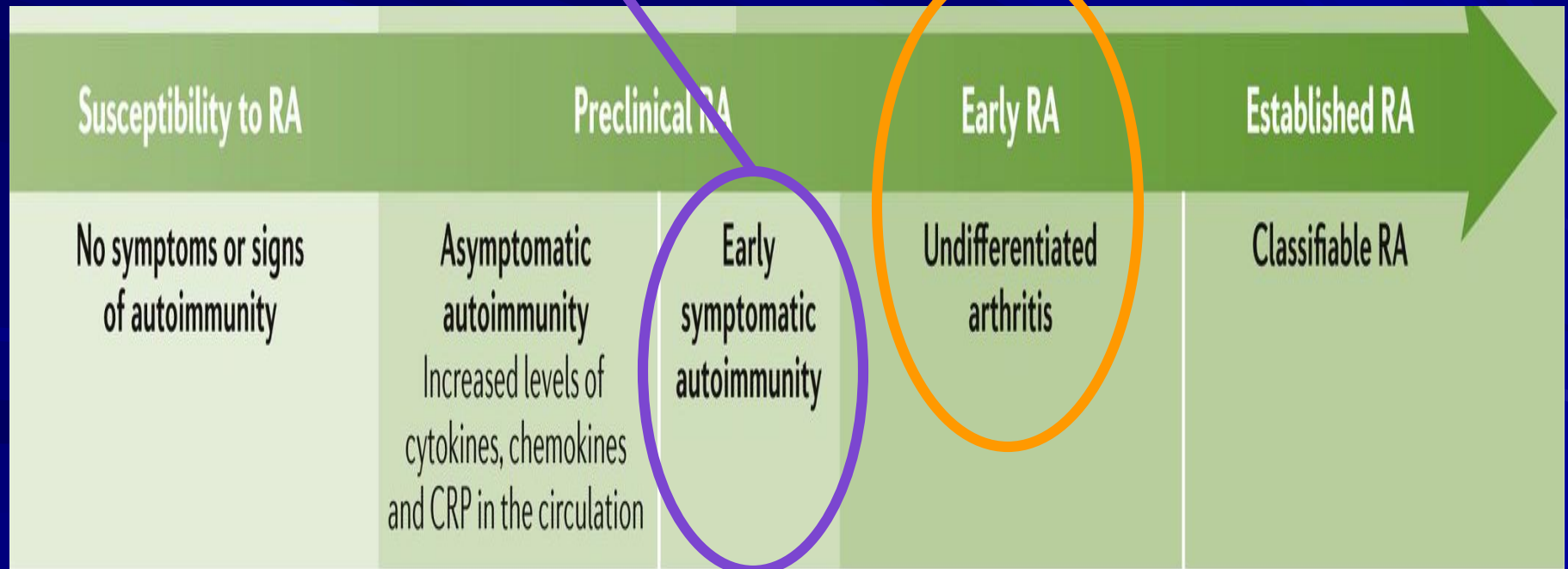
- RA development in 40% of the MTX group versus 53% of the placebo group ($P = 0.45$)

MTX postpone diagnosis of RA, not prevent it

- In the placebo group, all patients whose disease had progressed to RA within 1 year, versus only one-half of the RA patients in the MTX group ($P = 0.04$)

PRAIRI

PROMPT



PRAIRI study

Results after 2 years

RA development: 14/41 (34%)

Median time: 17 month

N=81

Arthralgia
+
(ACPA or RF)
+
(CRP or US/MRI)

Single infusion of
rituximab 1000mg

Placebo infusion

RA DELAYED

NOT

PREVENTED

RA development: 16/40 (40%)

Median time: 12 month

Table 2 | **Selected pharmacological prevention trials in RA**

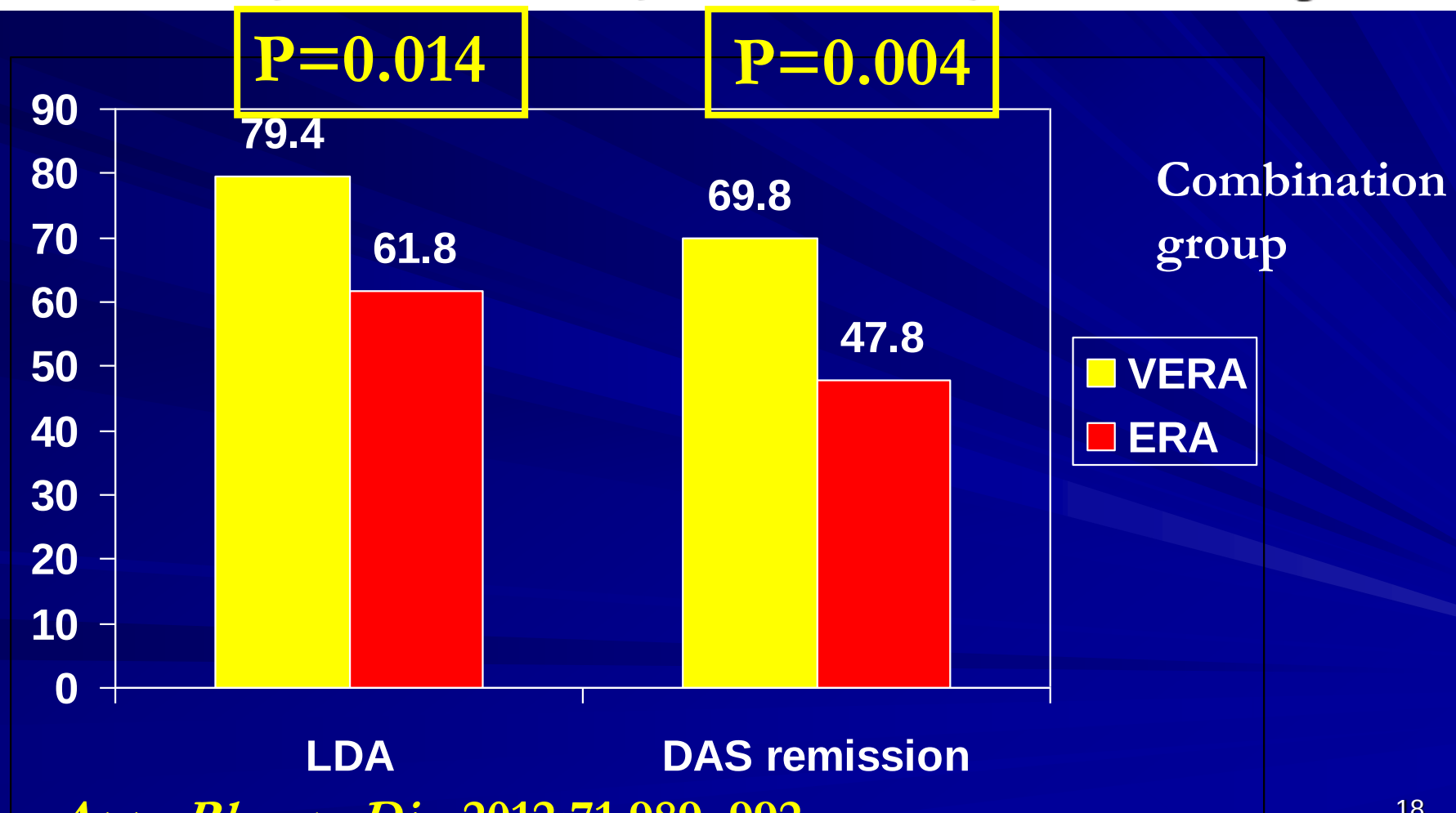
Study	Intervention	Duration; n	Study population	Results
PROMPT ^{133,255}	MTX (weekly oral administration) versus placebo	12 months; n=110	Undifferentiated arthritis, defined as symptoms of inflammatory arthritis for <2 years without meeting classification criteria for RA	RA development in 40% of the MTX group versus 53% of the placebo group ($P < 0.05$)
PRAIRI ²⁵⁶	Rituximab (one i.v. administration) versus placebo	24 months, n=81	Either presence of arthralgias plus presence of ACPAs and/or rheumatoid factor and increased acute-phase reactant levels or presence of synovitis on MRI	RA development was 34% in the rituximab group and 40% in the placebo group ($P > 0.05$); time to diagnosis of 25% of patients was 24 months in the rituximab group versus 12 months in the placebo group ($P > 0.05$); nonsignificant difference suggests a delay rather than prevention of RA

ADJUST ²⁵⁷	Abatacept (for 6 months) versus placebo	12 months; n=24	Adults with undifferentiated RA meeting exactly 1 of the 1987 ACR criteria for RA classification ²⁵⁸	RA development was delayed but not prevented
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STOP-RA ²⁵⁹	Hydroxychloroquine (daily) versus placebo	12 months n=200 ^a	High levels of ACPAs	Enrolling
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Combination etanercept and methotrexate provides better disease control in very early (≤ 4 months) versus early rheumatoid arthritis (> 4 months and < 2 years): post hoc analyses from the COMET study

Paul Emery,^{1,2} Tore K Kvien,³ Bernard Combe,⁴ Bruce Freundlich,⁵ Deborah Robertson,⁶ Tahmina Ferdousi,⁶ Eustratios Bananis,⁶ Ronald Pedersen,⁶ Andrew S Koenig⁶



Summary of studies supporting that early treatment of RA results in improved outcomes

- Linden, et al: treatment of RA within 3 months of symptom onset was associated with *increased chance of DMARD-free remission* and less joint destruction⁺
- Woude, et al: Data from two large early arthritis cohorts demonstrated that *sustained DMARD-free remission of RA* was significantly associated with shorter duration of symptoms of IA at time of initiation of therapy[‡]

⁺ **Arthritis & Rheumatism 2010;62(12):3537–46.**

[‡] **Arthritis & Rheumatism 2009;60(8):2262–71.**

Window of opportunity

- Early RA is thought to offer a window of opportunity whereby the disease is more sensitive to treatment and during which therapeutic intervention has the potential to alter the disease course (with preventing joint damage, decreasing functional disability, and inducing clinical remission)or even reversed with a complete return to normality

■ Definitions

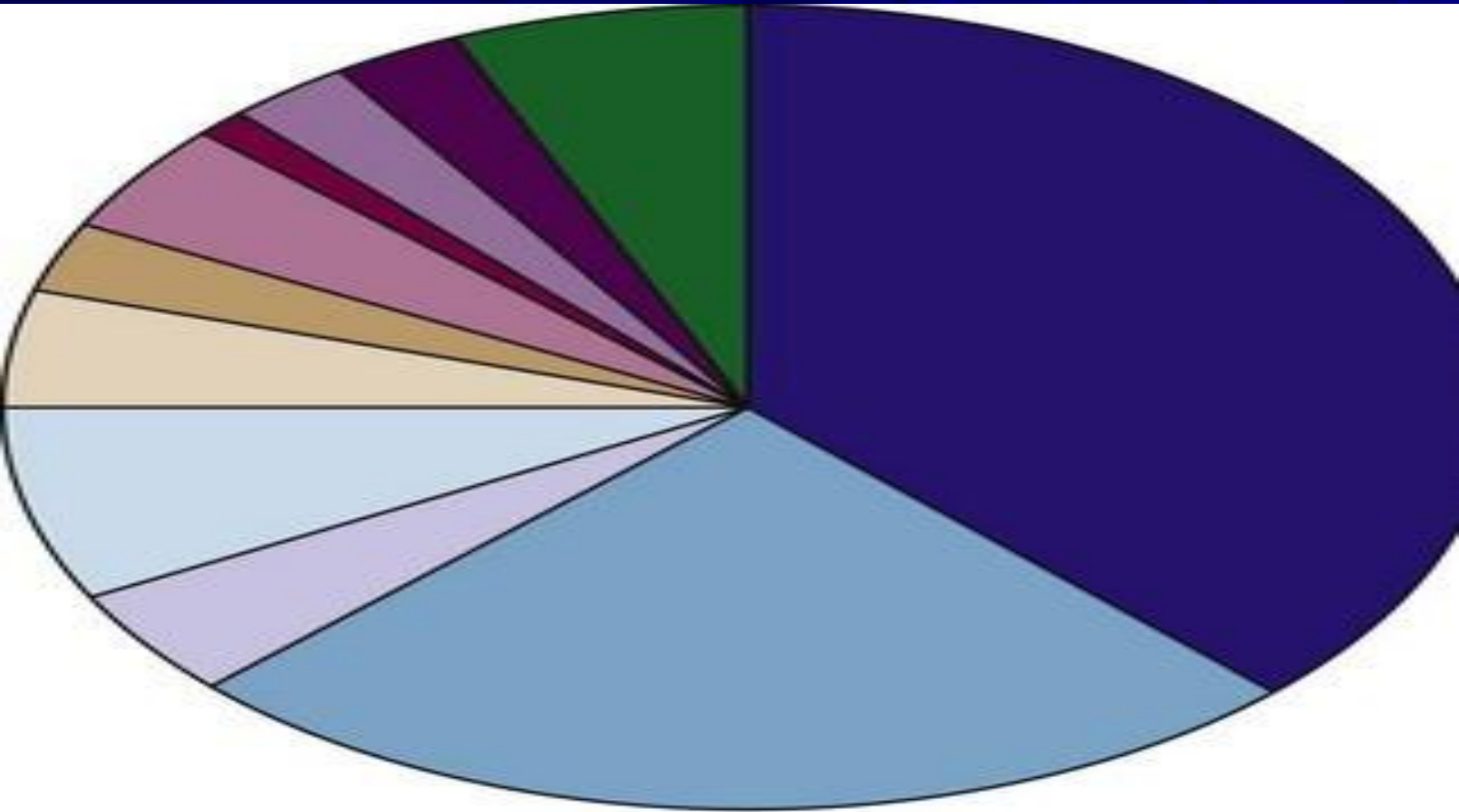
■ Importance

■ **Diagnosis**

■ Predictive response to treatment

- Many very early RA patients may present with UA
- Many very early UA patients experience spontaneous remission (40-45% vs 10-15% of RA)
- Treating all patients with very early synovitis might unnecessarily expose some to potentially toxic therapies

Overview of diagnoses of early arthritis patients after 1 year of follow up



- 1. Rheumatoid arthritis
- 2. Undifferentiated arthritis
- 3. Spondyloarthropathy

What are predictors of persistence and RA?

- Female gender: development risk RA is twofold higher in women than men
- Age: the incidence of RA is clearly age dependent
- Cigarette smoking
- Duration of symptoms
- BMI??
- FH?

Landewé R. J Rheumatol Suppl. 2007;80:8-15.

Rooy DP. Rheumatology (Oxford) 2011; 50: 93–100.

- Tender and swollen joint count: polyarthrititis have a 1.5-3fold higher likelihood of subsequently fulfilling the criteria for RA compared to patients with mono- or oligoarthrititis
- Hand involvement
- Level of acute phase response: CRP levels >50 mg/L have a fivefold increased risk of RA

■ Presence of RF and citrullinated ACPAs:

➤ In patients with synovitis of ≤ 3 months duration, a combination of sero-positivity for RF and anti-CCP Ab had a specificity of 97%, with a sensitivity of 63% for RA development

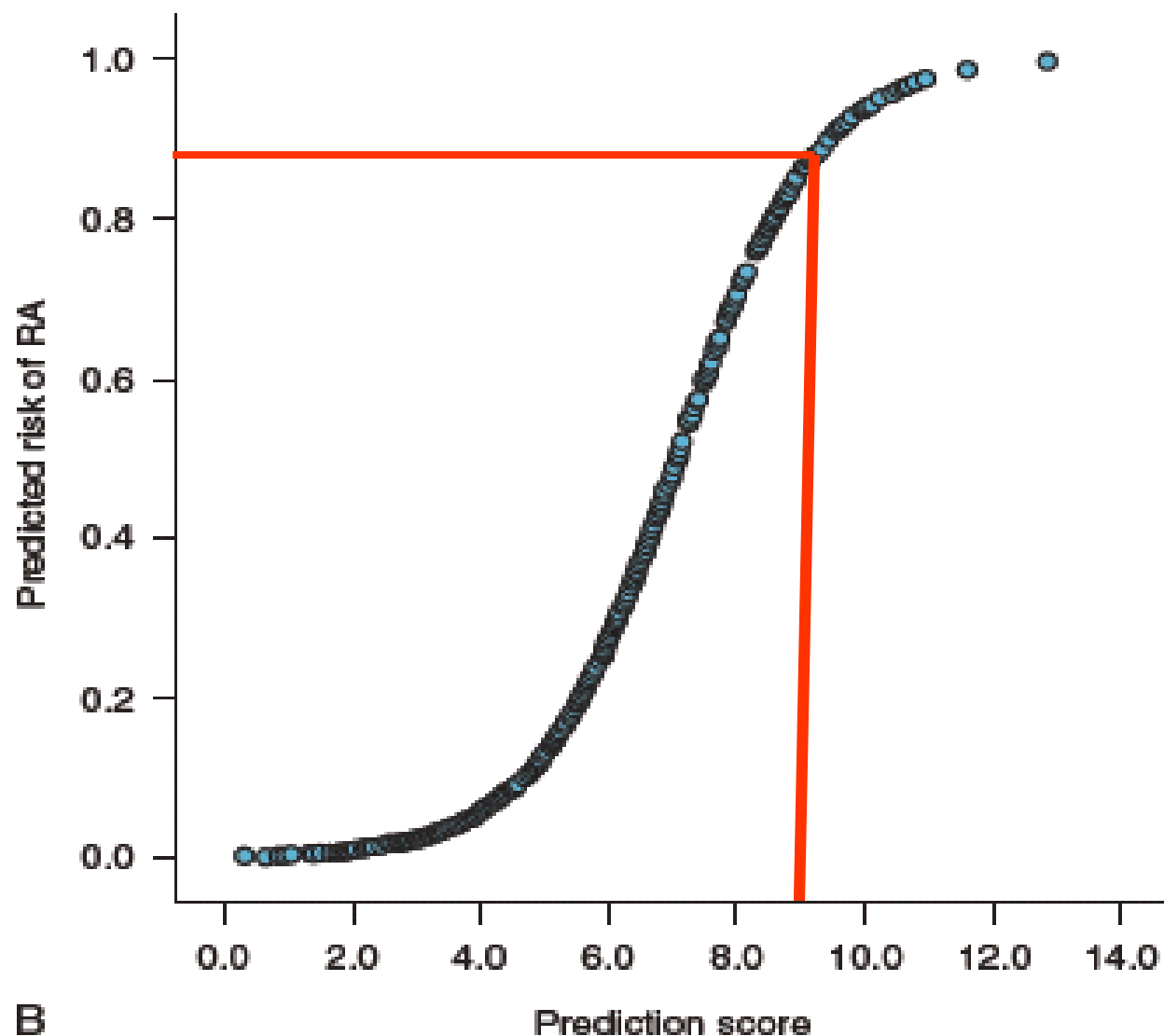
■ Genetic marker: HLA DRB1:(independent or in association with ACPAs ??)

Raza K, et al. Journal of Rheumatology. 2005; 32:231–238.

1. What is the age in years? Multiply by 0.02.		_____
2. What is the sex?		_____
In case female:	1 point	_____
3. What is the distribution of involved joints?		_____
In case small joints hands/feet:	0.5 point	_____
In case symmetric:	0.5 point	_____
In case upper extremities:	1 point	_____
In case upper and lower extremities:	1.5 points	_____
4. What is the score for morning stiffness on a 100-mm VAS?		_____
In case 26-90 mm:	1 point	_____
In case >90 mm:	2 points	_____
5. What is the number of tender joints?		_____
In case 4-10:	0.5 point	_____
In case 11 or higher:	1 point	_____
6. What is the number of swollen joints?		_____
In case 4-10:	0.5 point	_____
In case 11 or more:	1 point	_____
7. What is the C-reactive protein level?		_____
In case 5-50 mg/liter:	0.5 point	_____
In case 51 mg/liter or higher:	1.5 points	_____
8. Is the patient rheumatoid factor positive?		_____
If yes:	1 point	_____
9. Are the anti-CCP antibodies positive?		_____
If yes:	2 points	_____
	Total score	_____

Annette H, et al. *Arthritis Rheum* 56:433–440, 2007.

Score ≤ 6 NPV=91%
Score ≥ 8 PPV=84%



Validation of a prediction rule for development of rheumatoid arthritis

- In 3 cohorts of patients with recent onset UA, from the UK, Germany, and The Netherlands, the prediction score were calculated.
- The NPV (for a prediction score ≤ 6) in these 3 cohorts was 83-86%, the PPV (for a prediction score ≥ 8) was 93-100%

EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis

Table 2 Sensitivities and specificities for the presence of arthralgia at risk of RA with the clinical expertise on CSA as reference

Number of parameters present	Sensitivity (%)	Specificity (%)
≥1	100.0	14.1
≥2	98.4	53.8
≥3	90.2	74.4
≥4	70.5	93.6
≥5	32.8	100.0
≥6	16.4	100.0
≥7	1.6	100.0

Predictive Response to Treatment

Rationales for personalized medicine

- The expanding array of drugs available for treating rheumatoid arthritis is creating challenges in drug selection for the individual patient
- Treatment selection is based on a “trial-and-error” approach
- 30-40% of patients didn't respond to targeted biologic
- Efficacy vary among different individuals and over time

Cont.

- Time on multiple ineffective medications:
 - ❖ affects the patient's quality of life
 - ❖ may lead to irreversible joint damage
 - ❖ exposes the patient to potential adverse events
 - ❖ waste of health care resources

SO

Considerable research effort has been applied to identifying predictors of drug response to allow more rational prescribing of the drug most likely to be effective in individual patients (**precision medicine**)

BIOMARKERS

- Standard clinical and laboratory biomarkers: age, smoking
- Pathophysiological biomarkers:
 - ❖ Genetic biomarkers: gene polymorphisms
 - ❖ Protein biomarkers: TNF α protein in joint fluid ,serum or peripheral-blood mononuclear cells
 - ❖ Flow cytometry biomarkers (low count of CD27+memory B cells emerged as a potential predictor of the response to rituximab)

Thierry Lequerré et al.. Joint Bone Spine 2018

TRAINING
1st patient population

Combination of biomarkers

VALIDATION
2nd patient population

Large-scale validation in different patients

Results to date have been disappointing because:

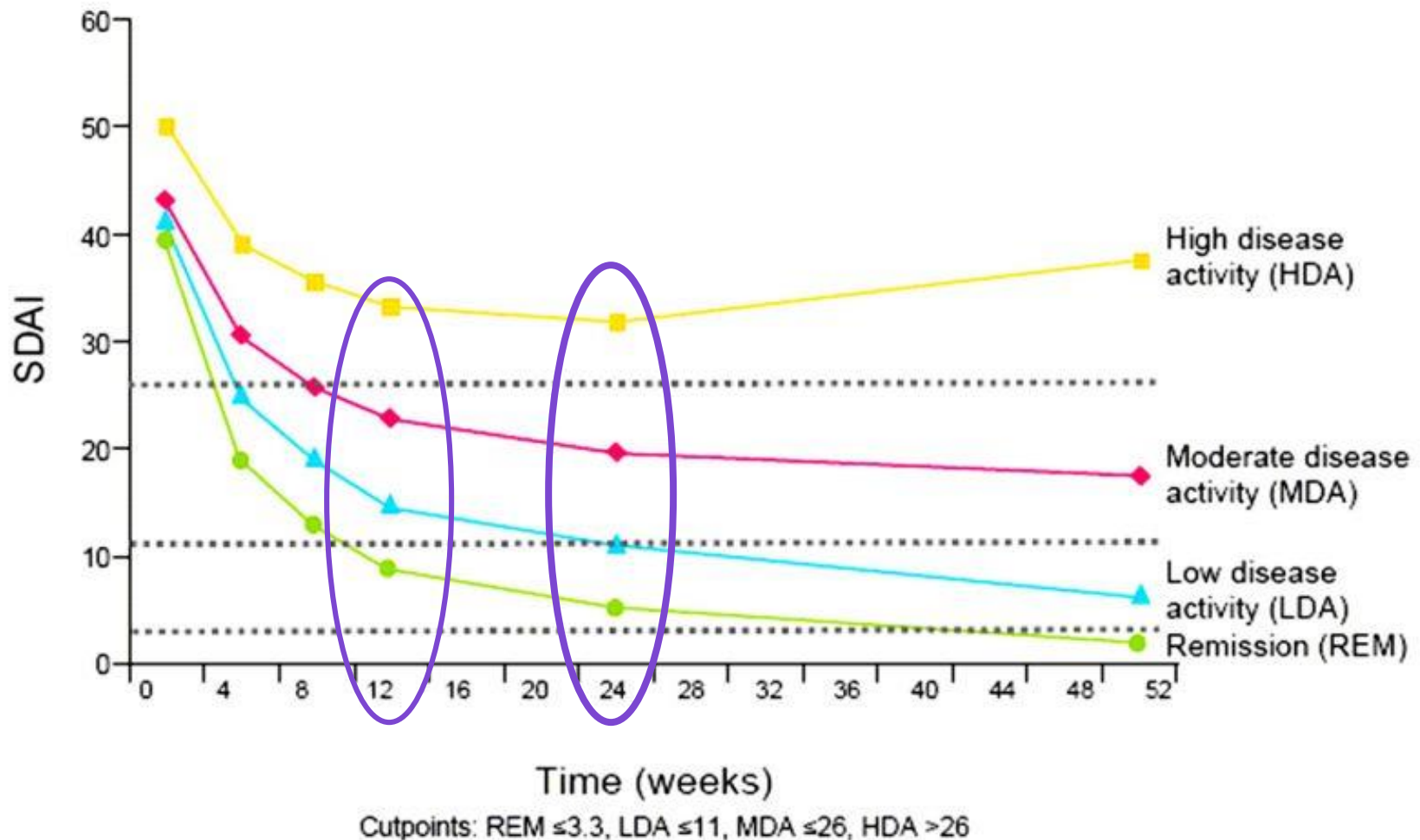
- Insufficient sample sizes(more than 1000)
- Different definition of response
- Tissue sampling
- Can predict the probability of response to a drug, but a lack of response cannot be predicted
- Adherence to therapy is a potential confounder of predictive studies
- The concentrations measured may not reflect their functional fraction

Forget personalised medicine and focus on abating disease activity

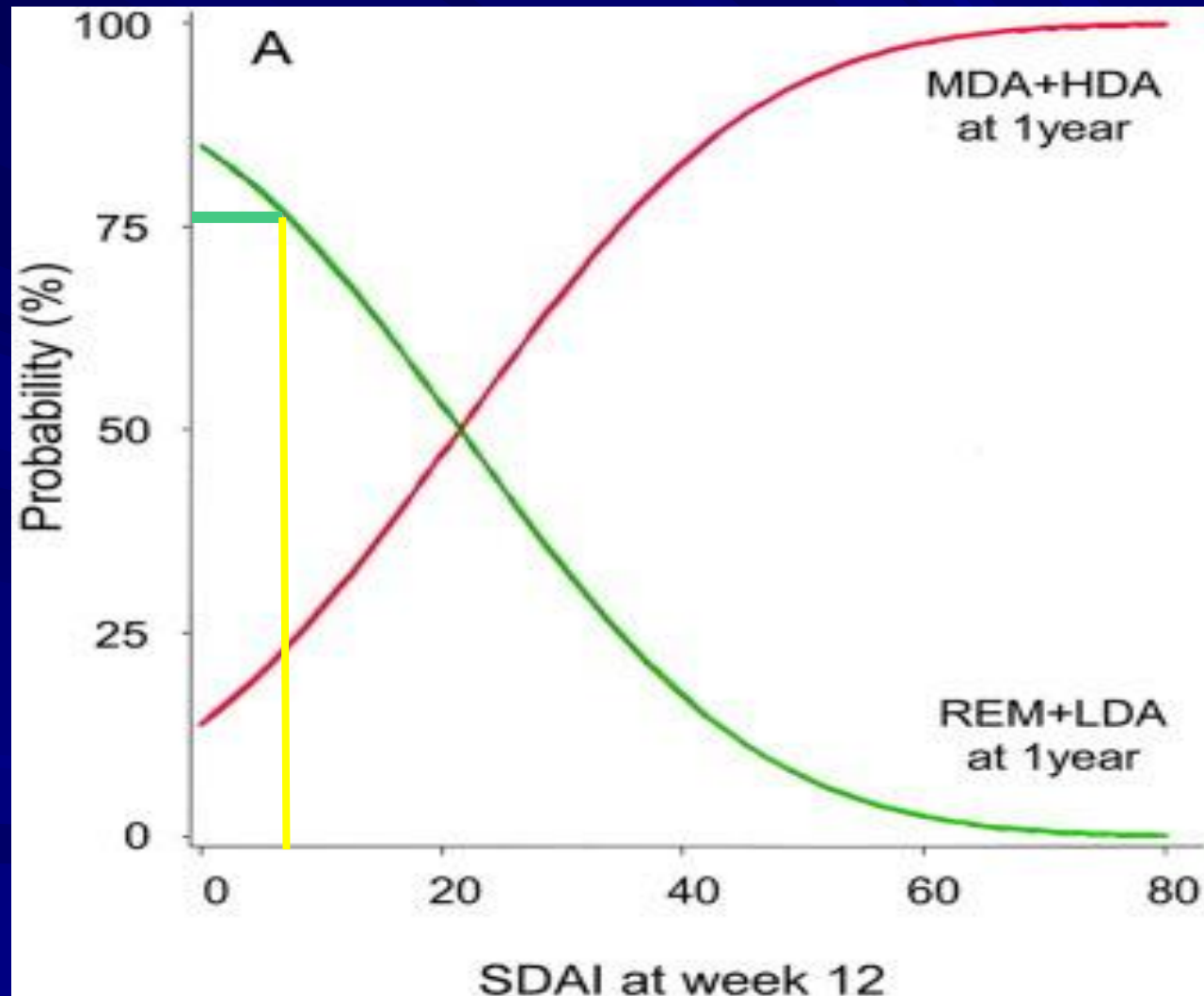
Josef S Smolen,^{1,2} Daniel Aletaha¹

Disease Activity Early in the Course of Treatment Predicts Response to Therapy After One Year in Rheumatoid Arthritis Patients

Daniel Aletaha,¹ Julia Funovits,¹ Edward C. Keystone,² and Josef S. Smolen³

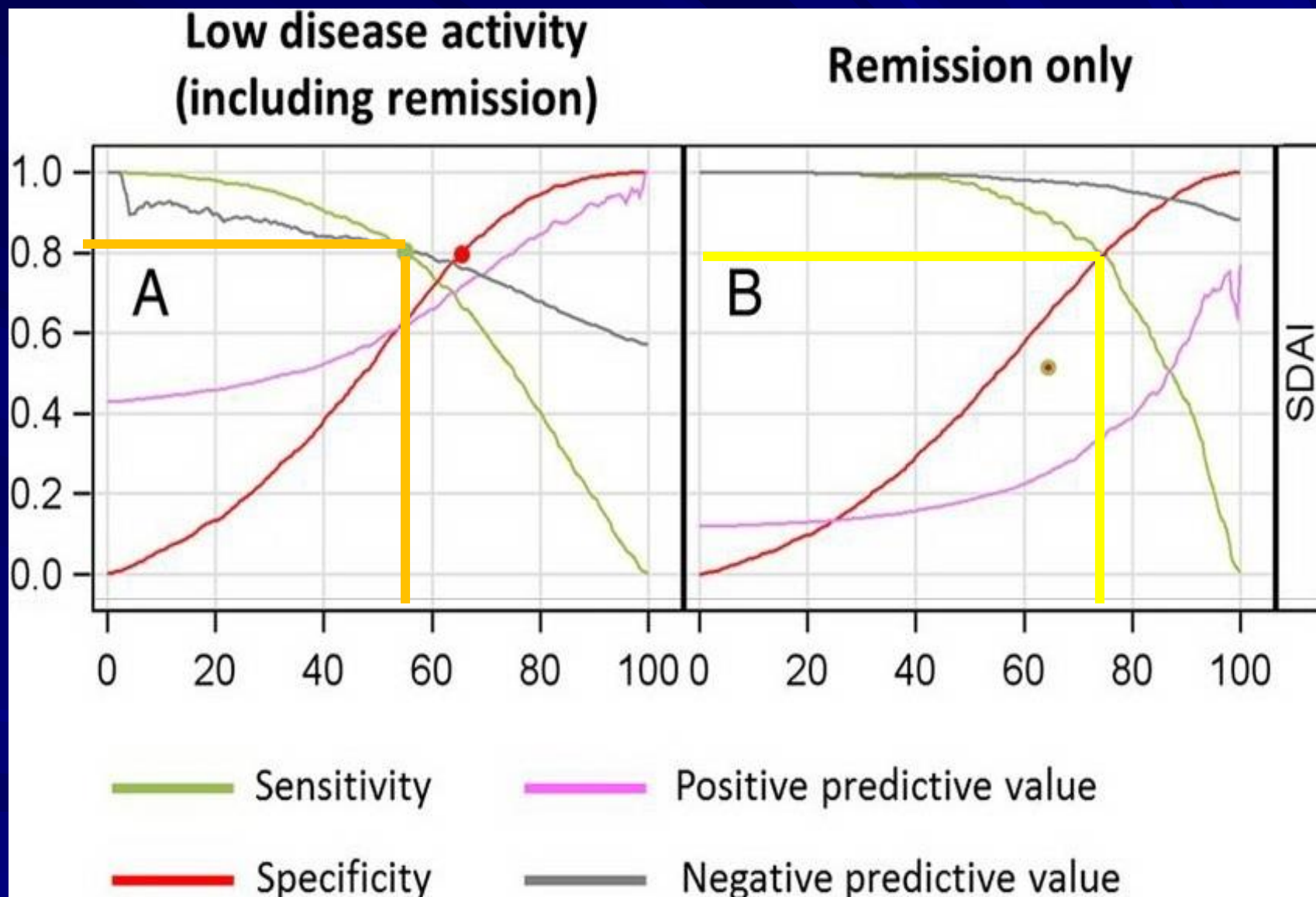


Disease activity early in the course of treatment predicts response to therapy after **one year** in rheumatoid arthritis patients



- Patients who have already significantly improved by 3 months will be the ones who should get the chance to show further improvement over the subsequent 3 month

What levels of improvement at 3 months are insufficient, and thus require treatment adaptations?



Aletaha D, et al. Ann Rheum Dis 2016;75:1479–1485.

Table 3

Prognostic implications of established response definitions

Response levels
observed at 3 months

TARGET=SDAI low disease activity (LDA) at 6 months

Definition	% (n/N)*	Sens.	Spec.	PPV	NPV	LR+	LR-
SDAI 50%	62.6% (1469/2347)	0.85	0.54	0.58	0.83	1.85	0.28
SDAI 70%	33.9% (796/2347)	0.59	0.85	0.75	0.74	4.00	0.48
SDAI 85%	14.2% (333/2347)	0.29	0.97	0.87	0.64	9.24	0.73

Take home messages

- Once arthritis present clinically, RA can Not be prevented
- In the absence of a definite diagnostic test, using prediction rule and ACR/EULAR 2010 help to distinguish patients need DMARDs therapy
- In the absence of strong response predictors of treatment, focus should be on reaching LDA/remission in the first 3-6 month of treatment

The background features a dynamic, abstract design with flowing, translucent blue and white shapes that create a sense of movement and depth. The colors transition from a deep blue on the left to a lighter, almost white on the right.

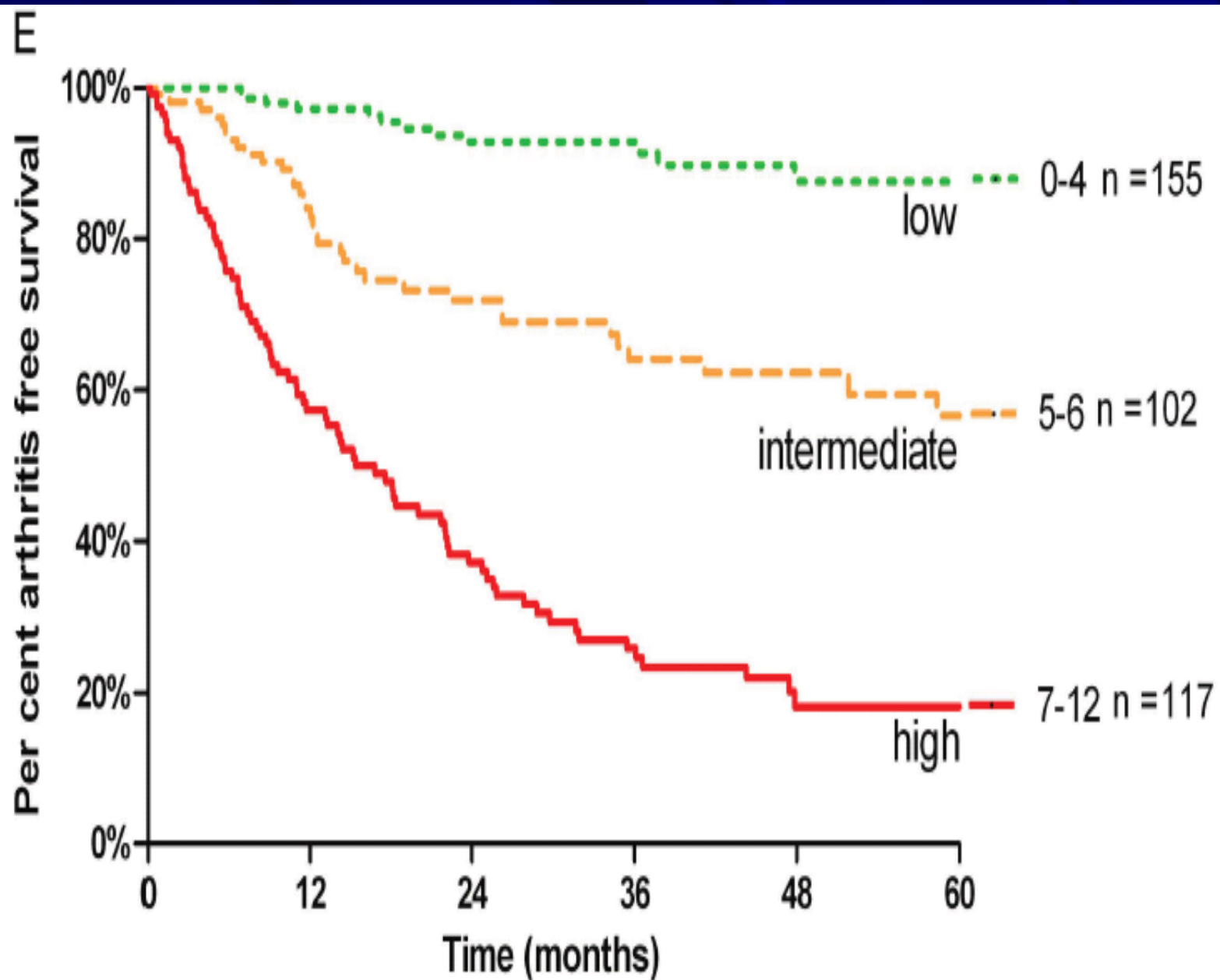
THANK YOU

A prediction rule for the development of arthritis in seropositive arthralgia patients

1. Does the patient have a first degree relative with rheumatoid arthritis? If yes 1 point_____
2. Does the patient drink alcohol? If no 1 point_____
3. Did the symptoms start less than 12 months ago? If yes 1 point_____
4. Are the symptoms intermittent? If yes 1 point_____
5. Are there symptoms in both upper and lower extremities? If yes 1 point_____
6. Is the VAS pain higher than or equal to 50? If yes 2 points_____
7. Does the patient have morning stiffness lasting more than or equal to one hour? If yes 1 point_____
8. Did the patient notice any swelling in a joint? If yes 1 point_____
9. Antibody status:
 - IgM-RF positive and aCCP negative 0 points
 - IgM-RF negative and aCCP positive < 3x cut-off 2 points
 - IgM-RF negative and aCCP positive $\geq$ 3x cut-off 3 points
 - IgM-RF and aCCP positive 4 points_____

Total _____

Points	Risk	Arthritis development				
		1 year	2 years	3 years	4 years	5 years
0 to 4 points	Low	3%	7%	7%	12%	12%
5 to 6 points	Intermediate	17%	29%	36%	38%	44%
7 to 13 points	High	43%	63%	74%	81%	81%



Which patients presenting with arthralgia eventually develop rheumatoid arthritis? The current state of the art

Debbie M Boeters,¹ Karim Raza,^{2,3} Annette H M vander Helm-van Mil^{1,4}

- A previous study has shown that US lesions (grey-scale synovial effusion or synovitis with or without power Doppler signal) are also present in the majority (88%) of healthy volunteers, it might be important to correct for normal, physiological findings when defining a positive US

Boeters DM, et al. *RMD Open* 2017;3. doi:10.1136/rmdopen-2017-000479

Challenges in Imaging in Preclinical Rheumatoid Arthritis

Daniel P. Marcusa, BA, Lisa A. Mandl, MD, MPH*

- In a cohort of 192 arthralgia patients without clinical arthritis but with a positive anti-citrullinated peptide antibody (ACPA) and/or IgM-RF, joints that were tender on examination or painful by history were scanned in 2 planes with both US and PD.
- Two blinded radiologists scored synovitis, joint effusions, and tenosynovitis on a semiquantitative scale

Rheum Dis Clin N Am 40 (2014) 727–734

- The positive predictive value (PPV) of pain predicting arthritis was 11%, and the negative predictive value (NPV) was 96%. However, when positive findings of synovitis on US and PD were both present, the PPV increased to 35%.

MRI of hand and foot joints of patients with anticitrullinated peptide antibody positive arthralgia without clinical arthritis

Annemarie Krabben,¹ Wouter Stomp,² Désirée M F M van der Heijde,¹

- In the follow-up period (mean 9 months (range 1– 15 months)), 12 arthralgia patients developed RA according to the 2010 American College of Rheumatology/European League Against Rheumatism
- **The combined inflammation scores between the arthralgia patients that did and did not develop RA were not different**