Inhibition of joint damage: a key target in RA

Genova, 21.10.2016

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OSTEO RHEUMATOLOGY 2016

Inhibition of joint damage: a key target in RA

- Rheumatoid Arhtirits: an erosive disease
- Effect of biological DMARDs on radiographic progression
- From the historical treatment approach to the *treat to target* strategy
- A step forward: the comprehensive disease control

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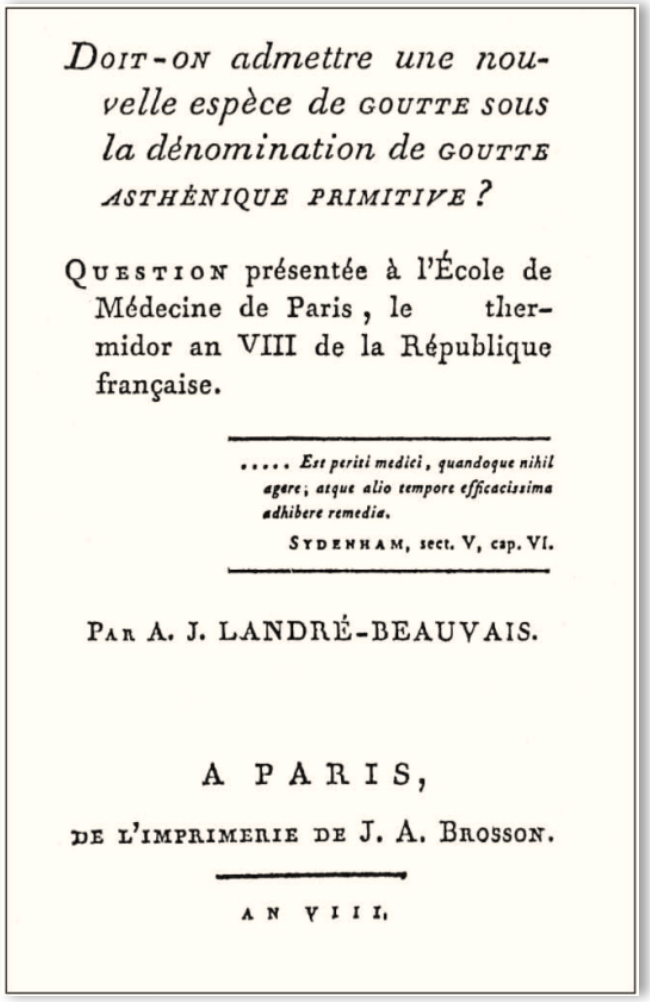
Joint damage in Rheumatoid Arthritis



DOIT-ON admettre une nouvelle espèce de GOUTTE sous la dénomination de GOUTTE ASTHÉNIQUE PRIMITIVE ?

QUESTION présentée à l'École de Médecine de Paris, le thermidor an VIII de la République française.

..... Est periti medici, quandoque nihil agere; atque alio tempore efficacissima adhibere remedia.

SYDENHAM, sect. V, cap. VI.

PAR A. J. LANDRÉ-BEAUVAIS.

A PARIS,

DE L'IMPRIMERIE DE J. A. BROSSON.

AN VIII.

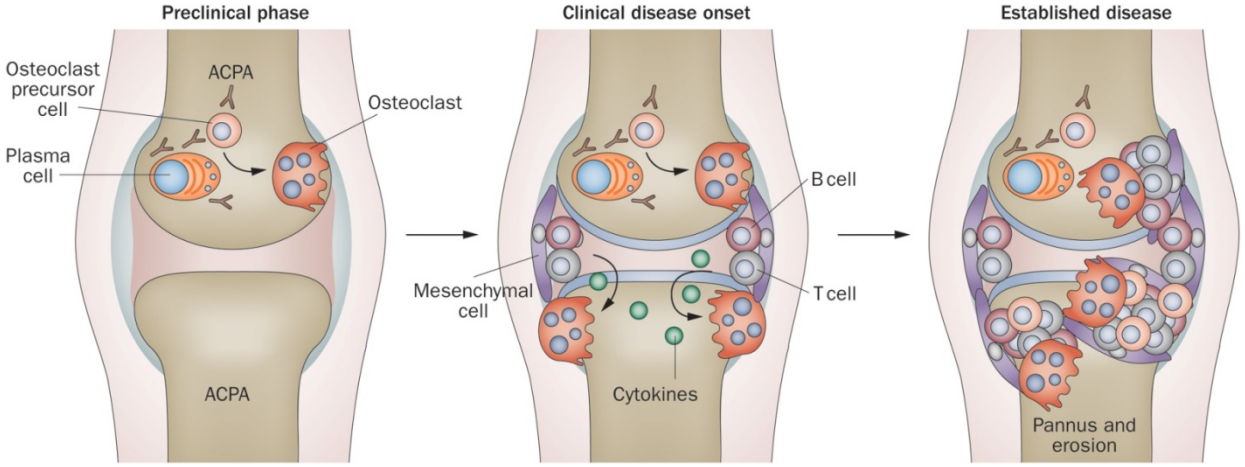
"A woman, who died at 68 years of age […]. When the body was opened, the ***wrist*** *was seen to be* ***misshapen, swollen and distorted****; the subcutaneous cellular tissue was extremely thick and compact; and the joint capsules and ligaments were noticeably thickened. When the inside of the joints was examined, the* ***joint cartilage of the forearm and carpal joints appeared severely disorganized****, been seen only as a sort of budding reddish tissue: the* ***heads of the bone were unevenly swollen and even carious in several place at their surface****"*

Joint Bone Spine 2001

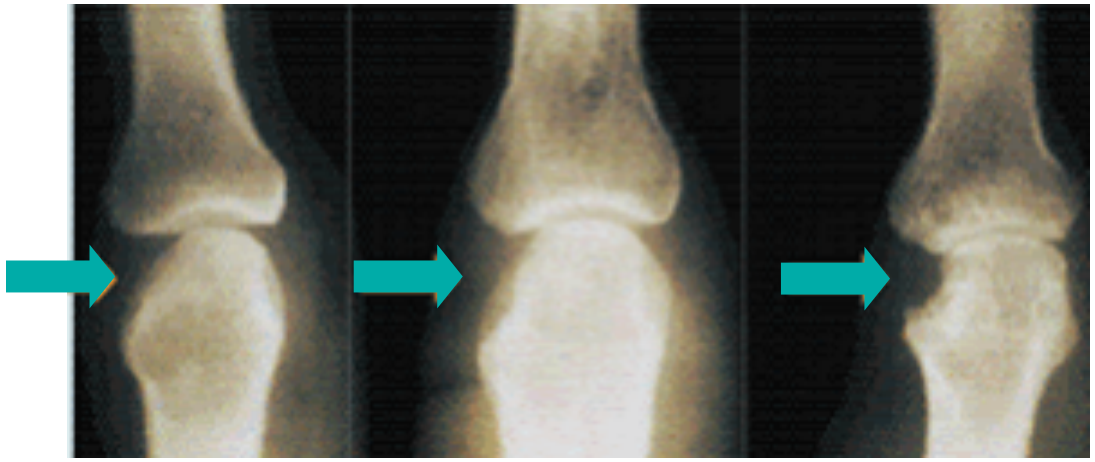
RHEUMATOID ARTHRITIS - CLASSIFICATION

Criterion		1987
Morning stiffness	1	At least 1 hour
Joint involvement	1	≥ 3 joints
Arthritis of hand joints	1	
Symmetric arthritis	1	≥ 1swollen joint
Rheumatoid nodules	1	
Serology	1	RF +
Radiographic changes	1	Erosions or decalcification in/adjacent to involved joints
Acute phase reactants	NA	
Duration of symptoms	NA	

Progression of joint damage in untreated RA



Schett G & Gravallese E. Nat Rev Rheumatol *2012*

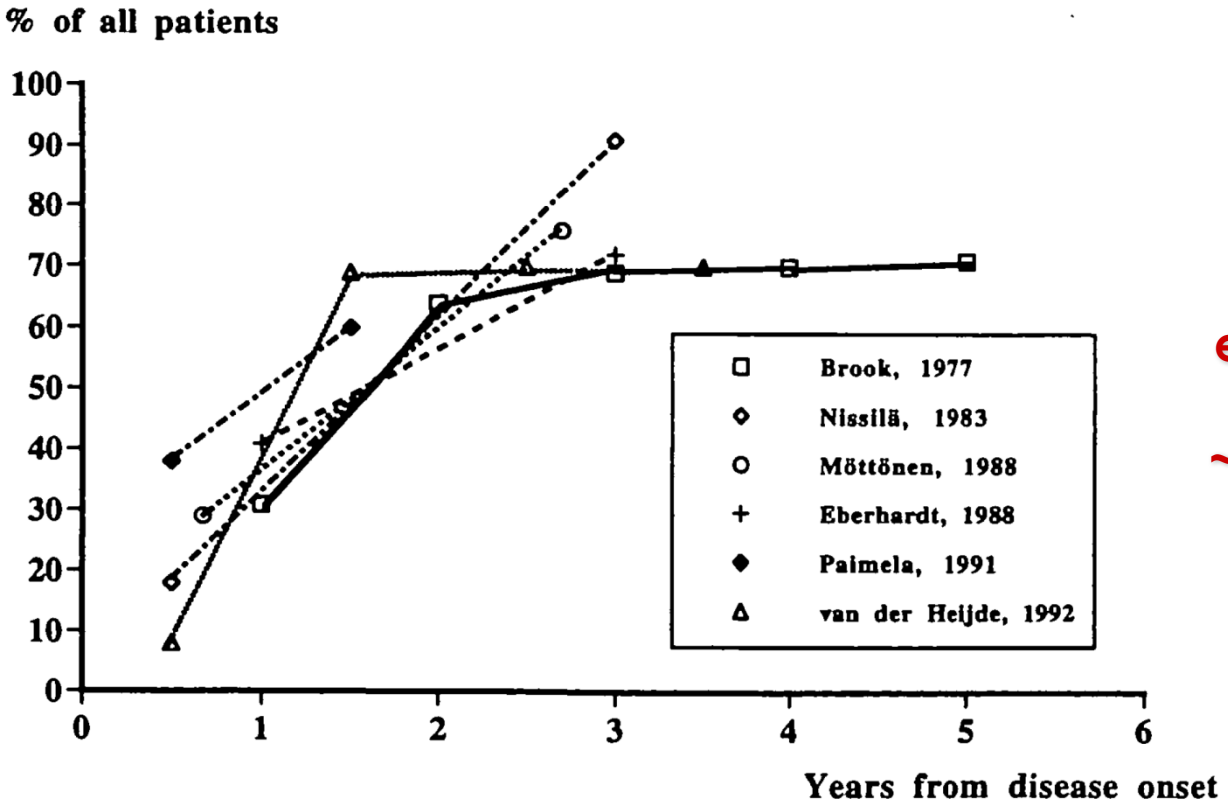


baseline **1 yr after** **2 yrs after**

"breaks in the cortical bone surface, accompanied by loss of the adjacent trabecular bone"

RHEUMATOID ARTHRITIS – OUTCOME (pre-bDMARDs)

the rate of radiographic progression is higher at the beginning of RA and declines in the later stages of the disease

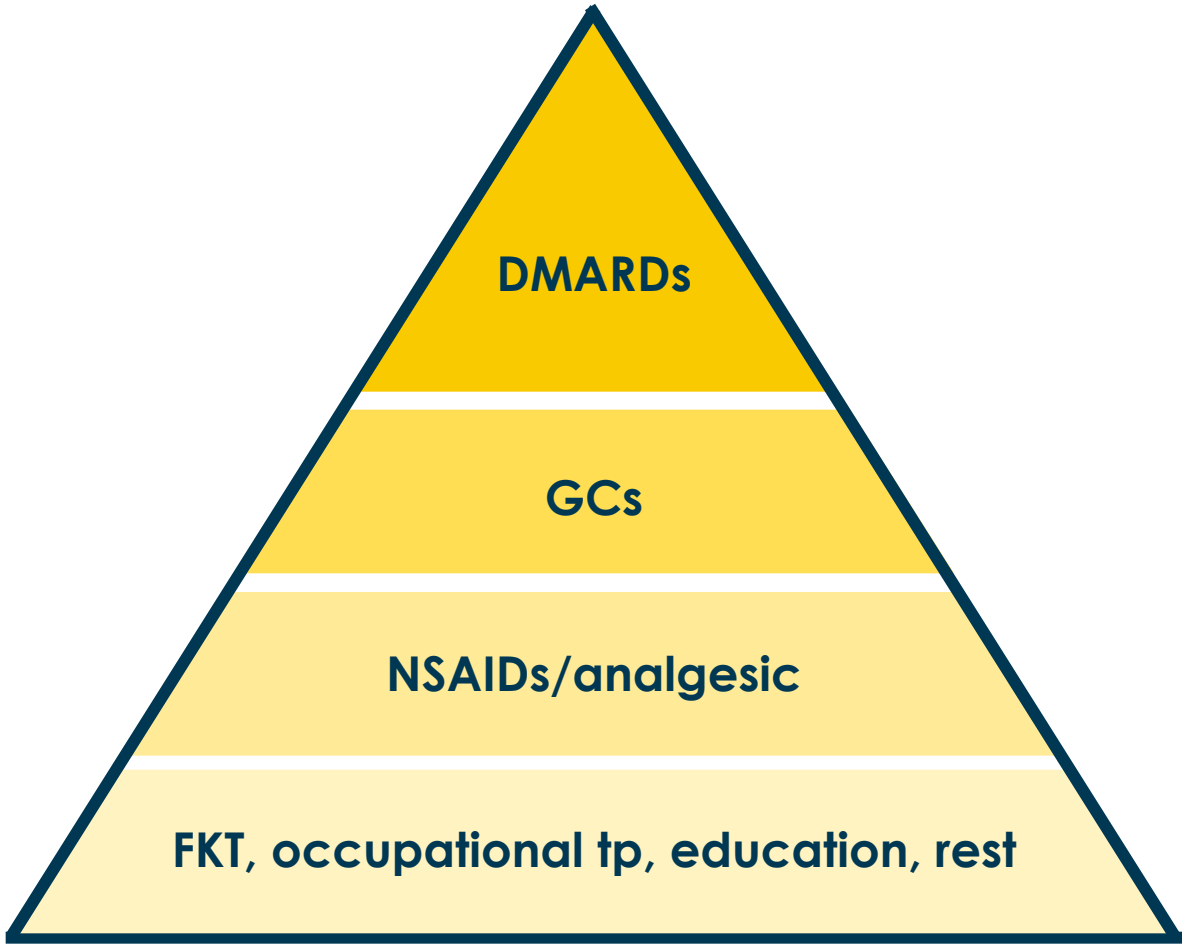


~50% of patients already has joint erosions at 6 months and ~70% at 2 years from the disease onset

Van der Heijde DMFM. Br J Rheumatol 1995

RHEUMATOID ARTHRITIS – TREATMENT (pre-bDMARDs)

the pyramid paradigm: "*GO LOW, GO SLOW*"



RHEUMATOID ARTHRITIS – TREATMENT GOALS

HISTORICAL APPROACH

Pain relief

Control of disease activity

"more toxic" drugs for refractory cases

1990s APPROACH

Control of disease activity

Emphasis on joint damage

Earlier intensive treatment (MTX, SSZ, combination therapy)

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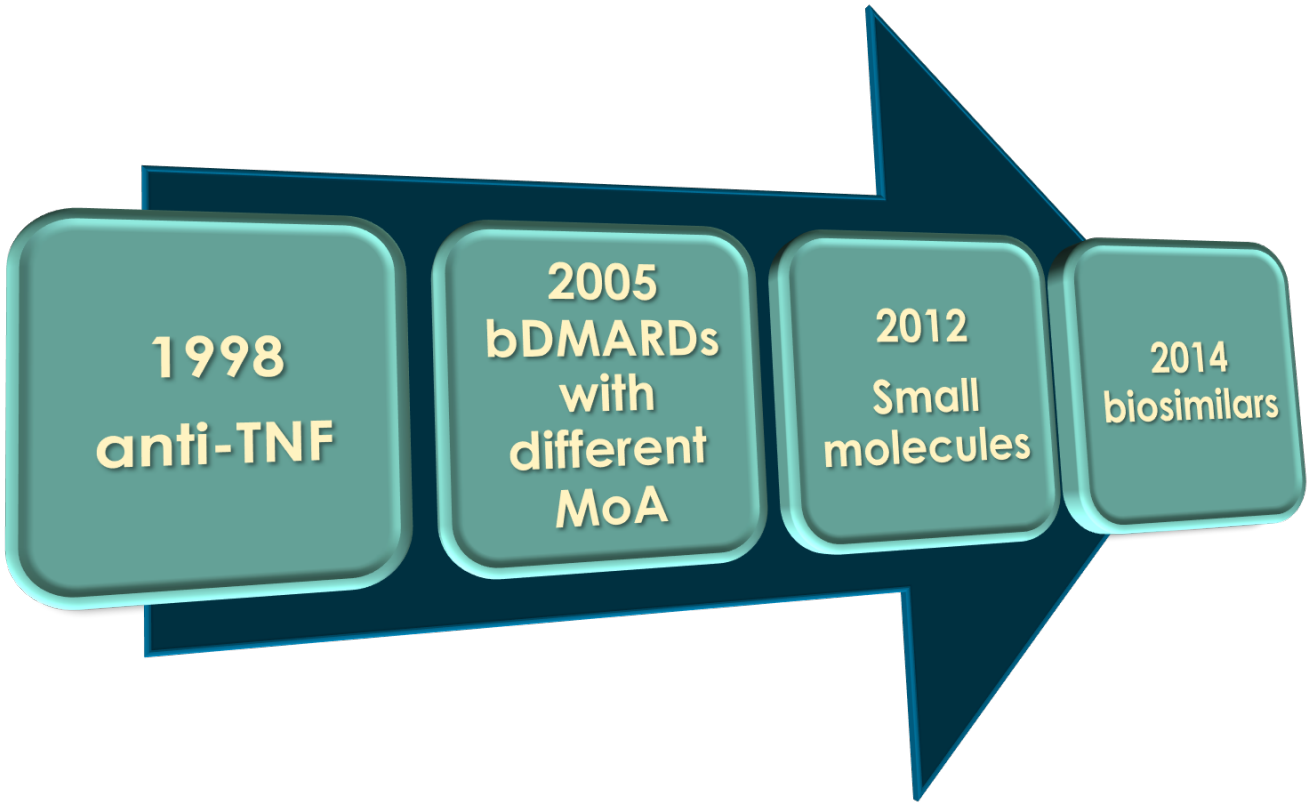
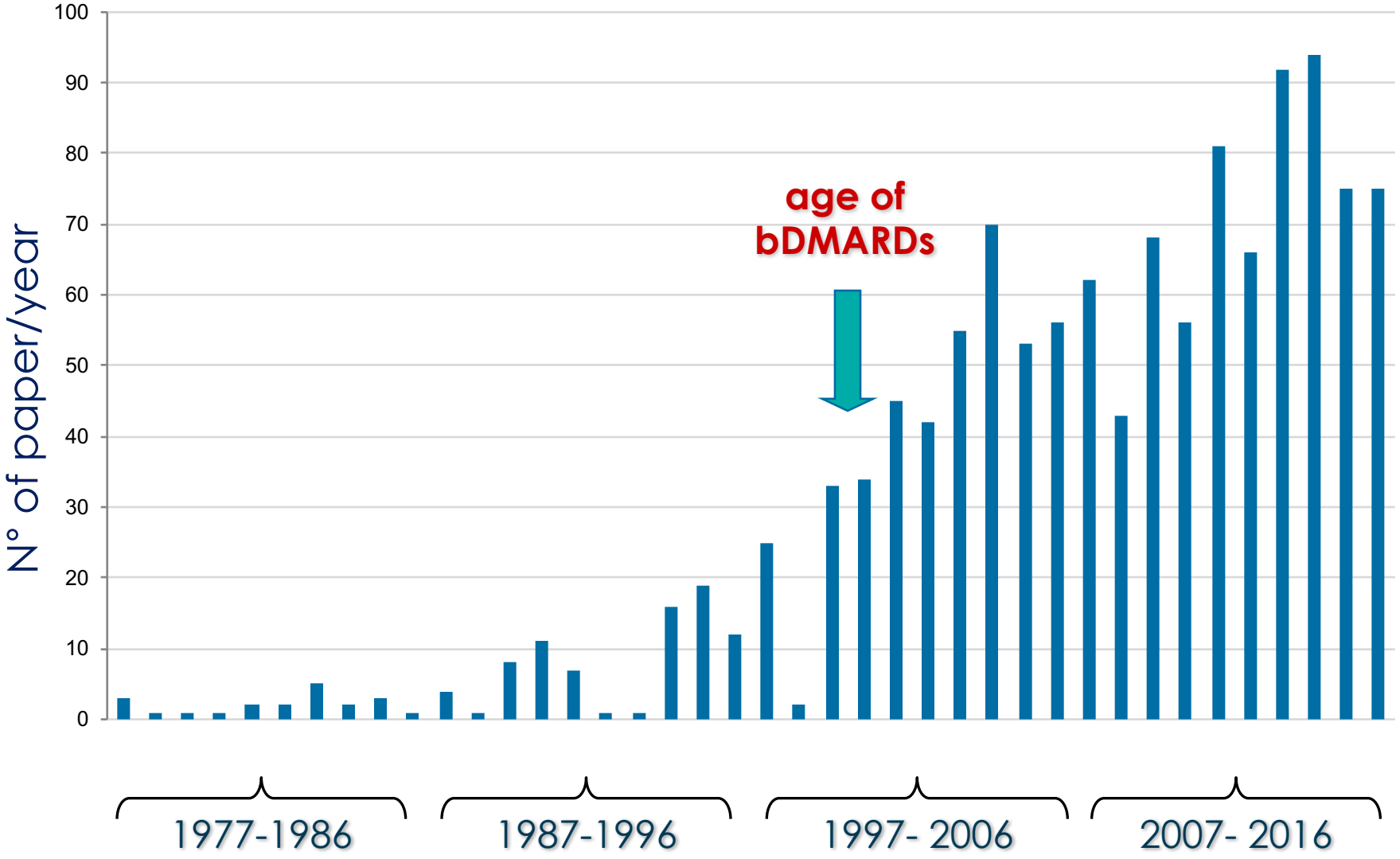
RHEUMATOID ARTHRITIS – TREATMENT (the age of bDMARDs)

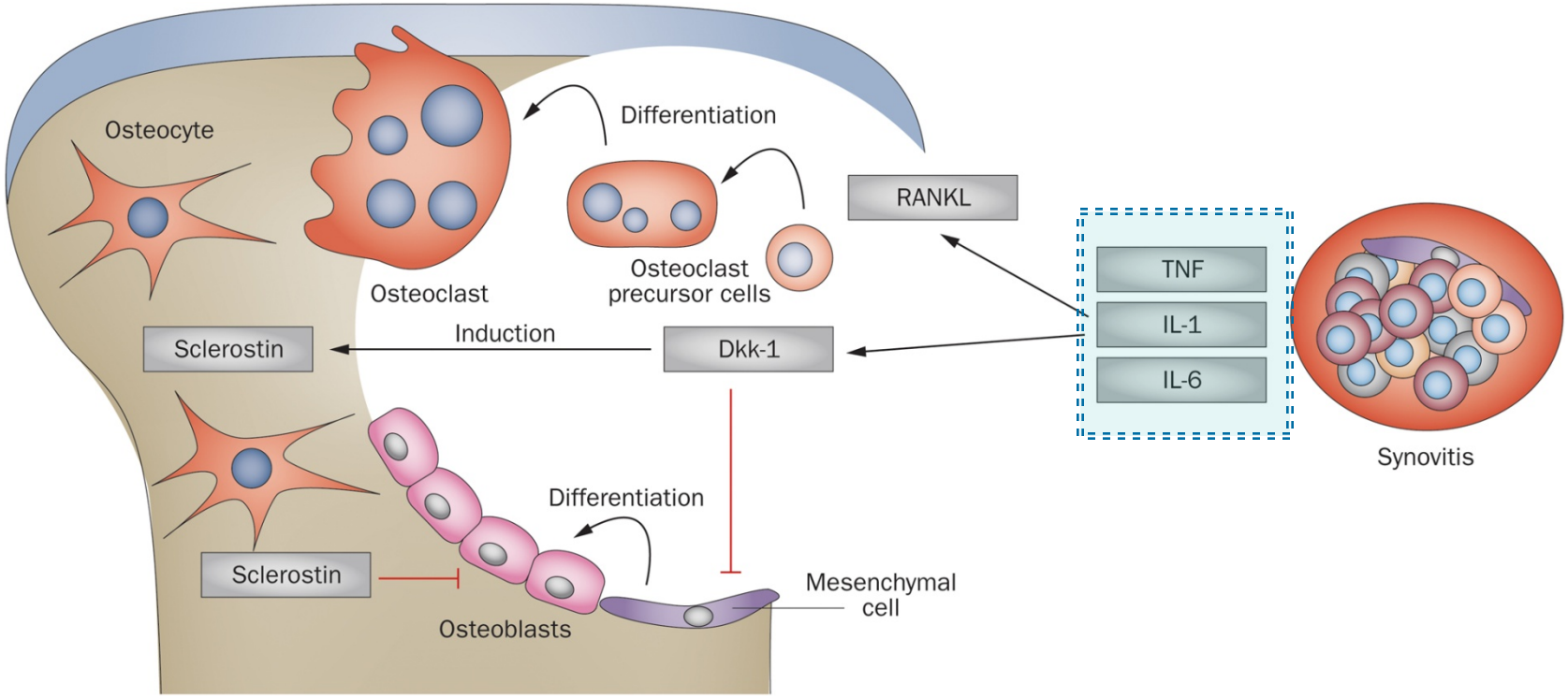


Pubmed search for “rheumatoid arthritis” AND “radiographic progression”



https://www.ncbi.nlm.nih.gov/pubmed/?term=rheumatoid%20arthritis%20radiographic%20progression

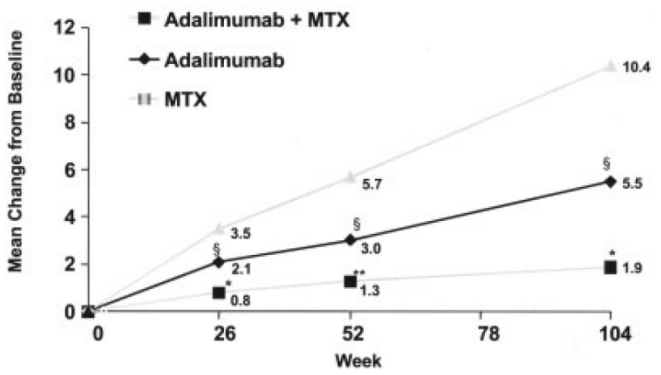
SYNOVITIS & BONE HOMEOSTASIS



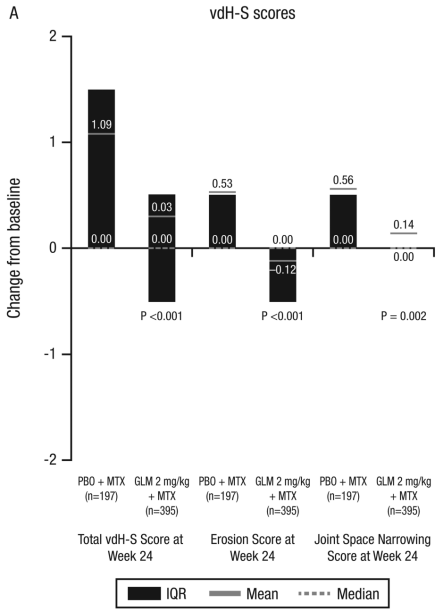
Schett G & Gravallese E, Nat Rev Rheumatol 2012

TNFi -combination therapy over MTX

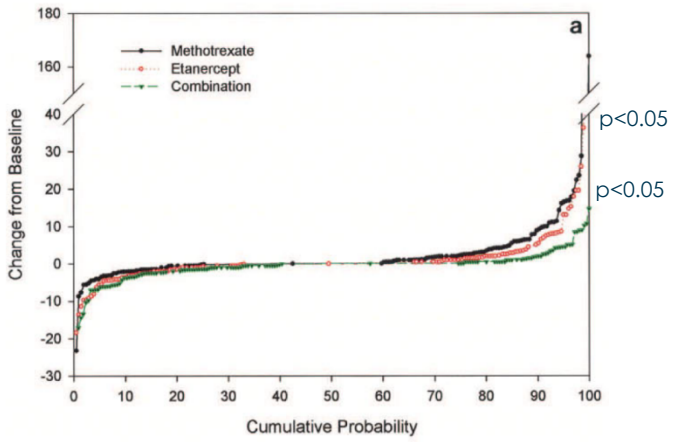
PREMIER (Ada) n=799



GO-FURTHER (Glm) n=592



TEMPO (Eta) n=686

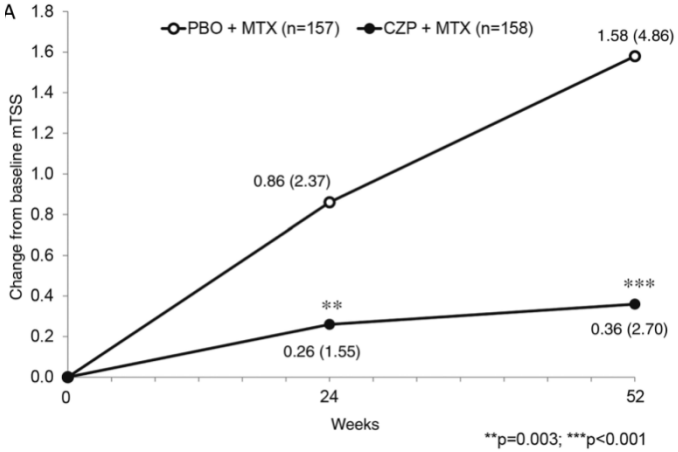


ASPIRE (Ifx) n=1049

Table 2. Change in radiographic scores*

	MTX + placebo (n = 282)	MTX + 3 mg/kg infliximab (n = 359)
Change in van der Heijde modification of the total Sharp score from baseline to week 54†		
Mean ± SD	3.7 ± 9.6	0.4 ± 5.8
Median (IQR)	0.43 (0.0, 4.5)	0.0 (−0.8, 1.3)
P‡		<0.001
Change in erosion score from baseline to week 54§		
Mean ± SD	3.0 ± 7.8	0.3 ± 4.9
Median (IQR)	0.3 (0.0, 3.8)	0.0 (−0.8, 1.3)
P‡		<0.001
Change in JSN score from baseline to week 54§		
Mean ± SD	0.6 ± 2.1	0.1 ± 1.6
Median (IQR)	0.0 (0.0, 0.4)	0.0 (0.0, 0.0)
P‡		<0.001

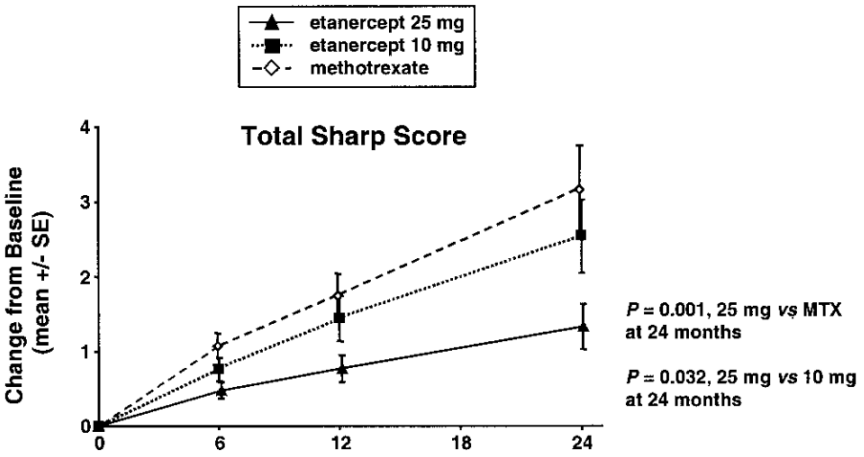
C-OPERA (Czp) n=315



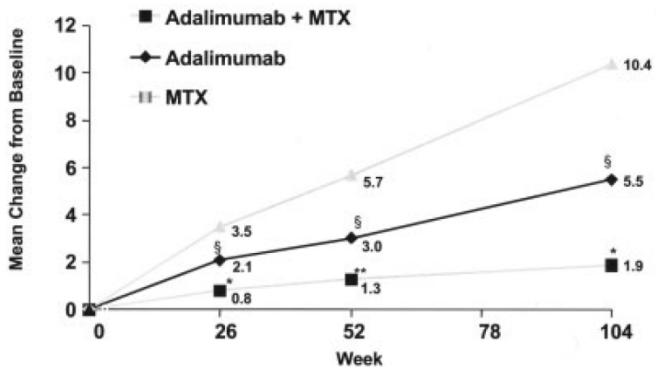
Breedveld FC t al 2006, Weinbltt EC et l 2013 van der Hejide D et al 2006, St Clarie et al 2004, Atsumi T et al 2016

TNFi monotherapy over MTX

ERA study (Eta)
n=632



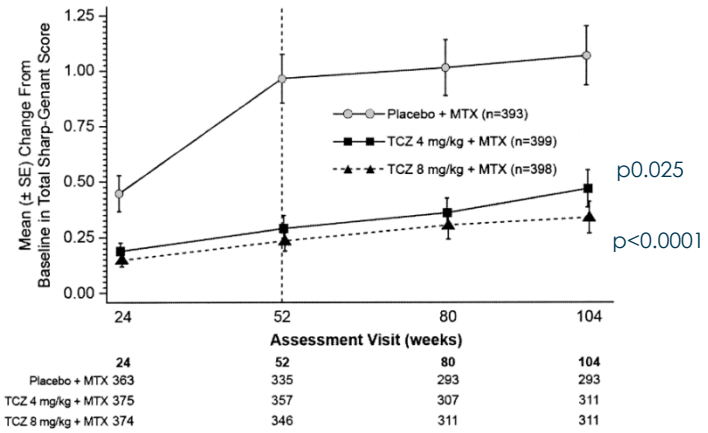
PREMIER (Ada)
n=799



Genovese M et al 2002, Breddveld FC et al 2006

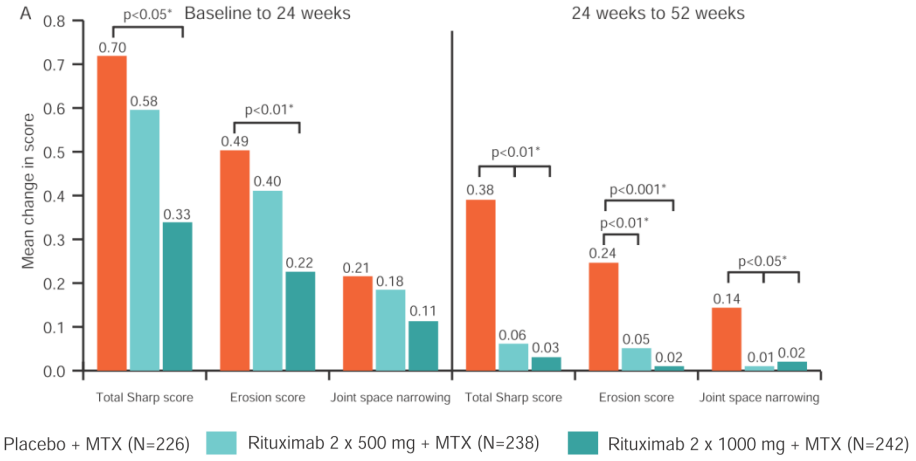
Non-TNFi bDMARDs

LITHE (Tcz) n=1190

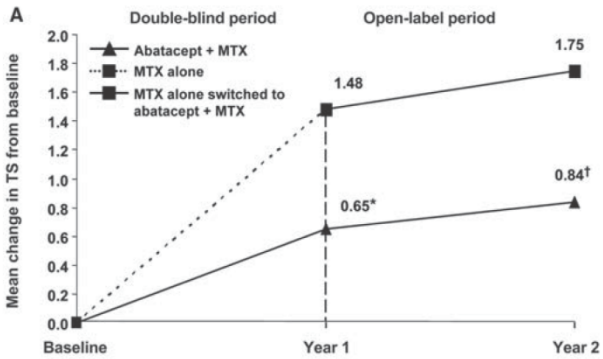


	24	52	80	104
Placebo + MTX	363	335	293	293
TCZ 4 mg/kg + MTX	375	357	307	311
TCZ 8 mg/kg + MTX	374	346	311	311

IMAGE (Rtx) n=715

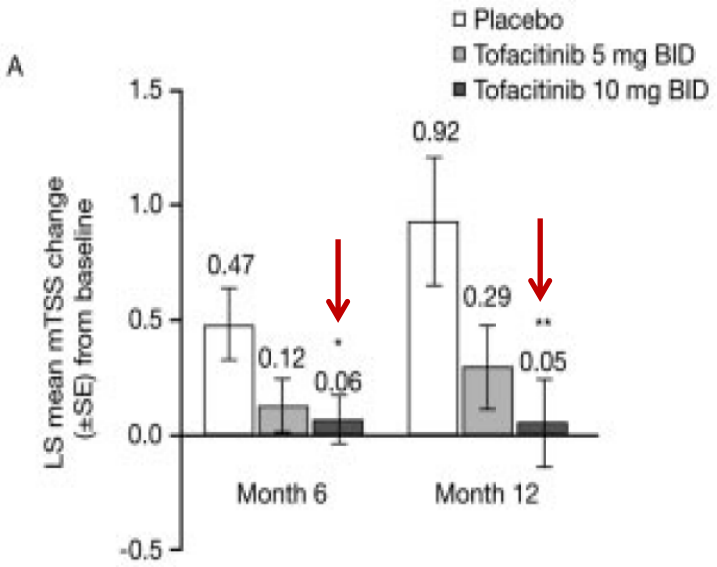


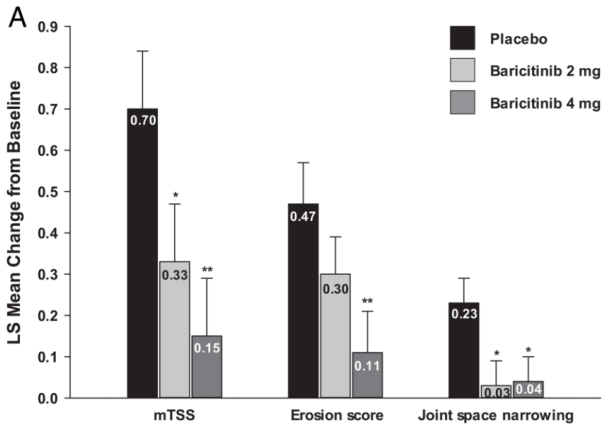
AGREE (Aba) n=410

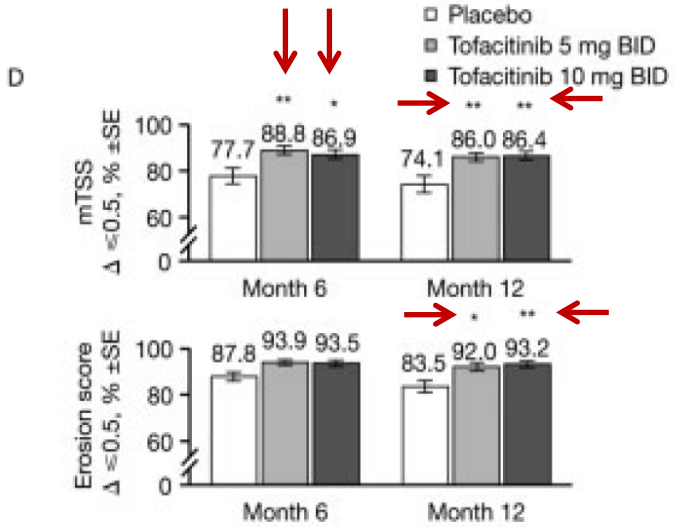


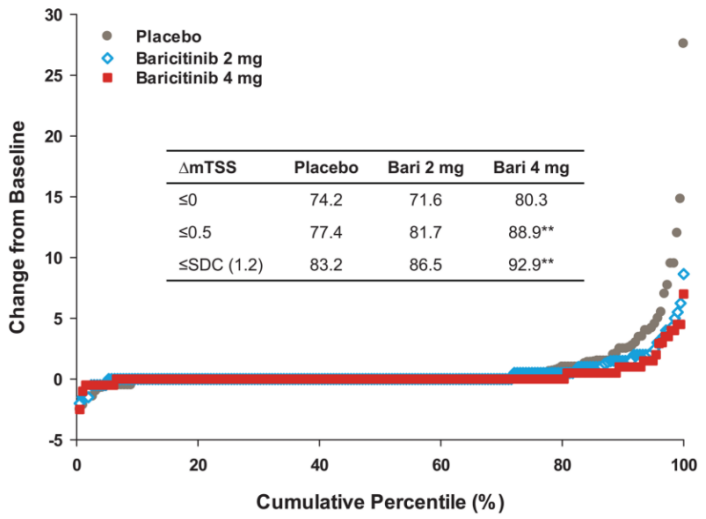
Fleisschmann RM et al 2013; Tak PP et al 2011; Bathon J et l 2011

JAK-inhibitors







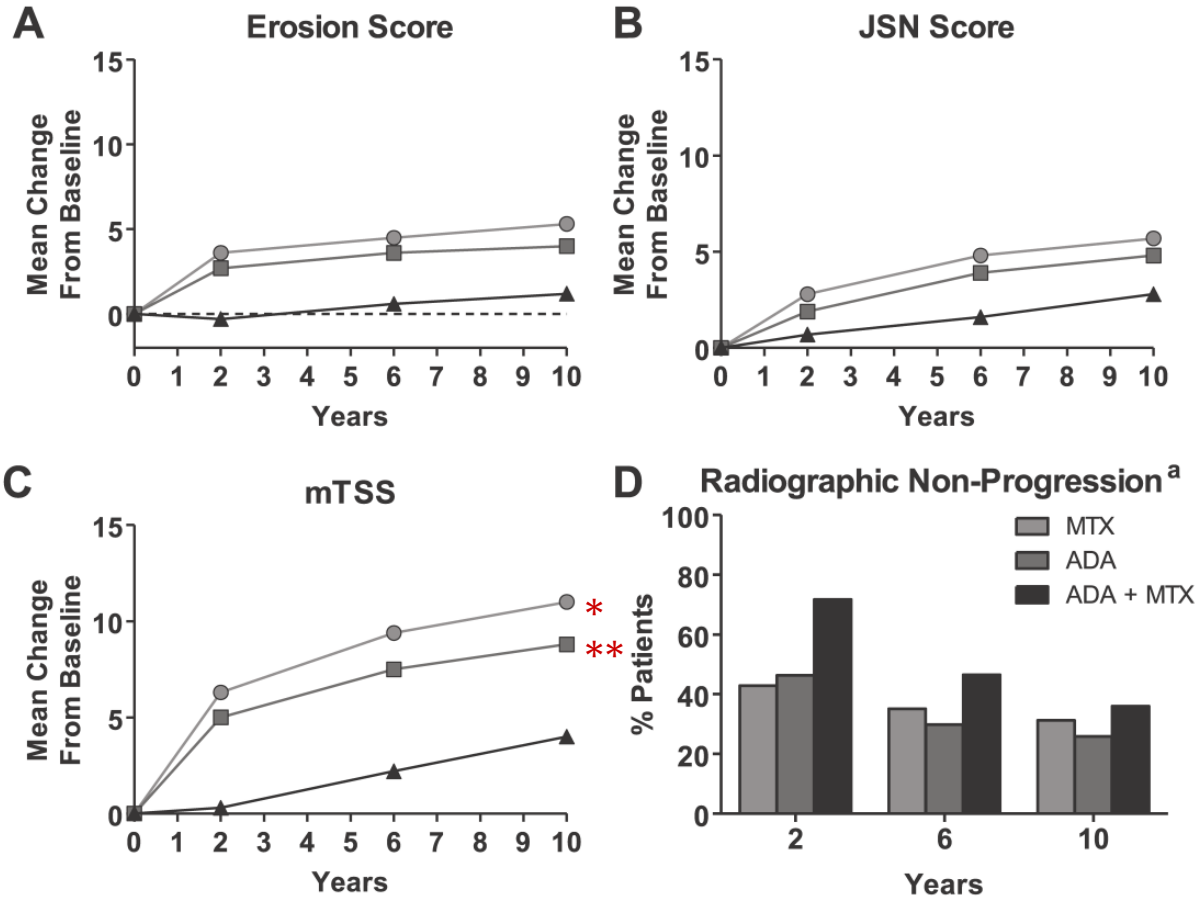


Van der Heijde D et al 2013

Dougados M et al 2016

Long-term effect

PREMIER (Ada)
n=250



*

*p=0.01, **p<0.001

Keystone EC et al 2014

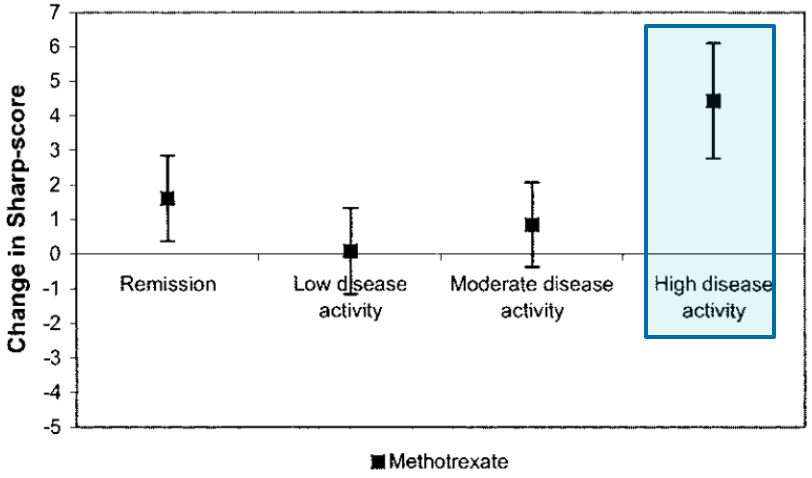
ARTHRITIS & RHEUMATISM
Vol. 54, No. 10, October 2006, pp 3119–3125

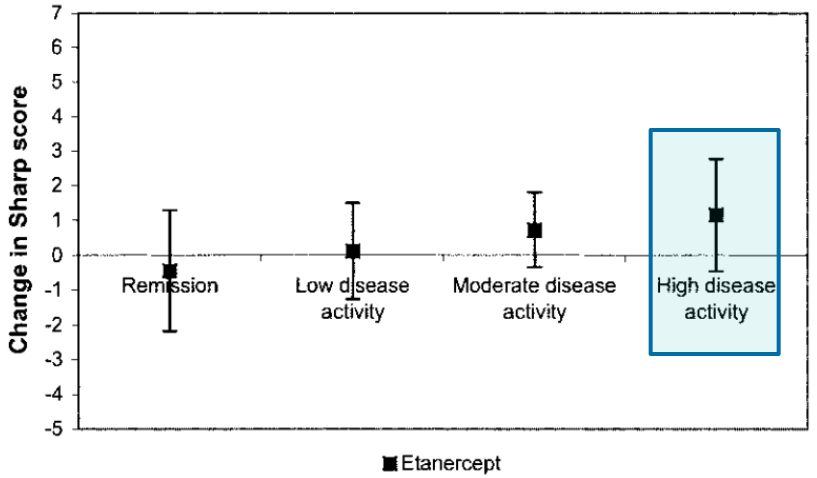
Disconnect Between Inflammation and Joint Destruction After Treatment With Etanercept Plus Methotrexate

Results From the Trial of Etanercept and Methotrexate With Radiographic and Patient Outcomes

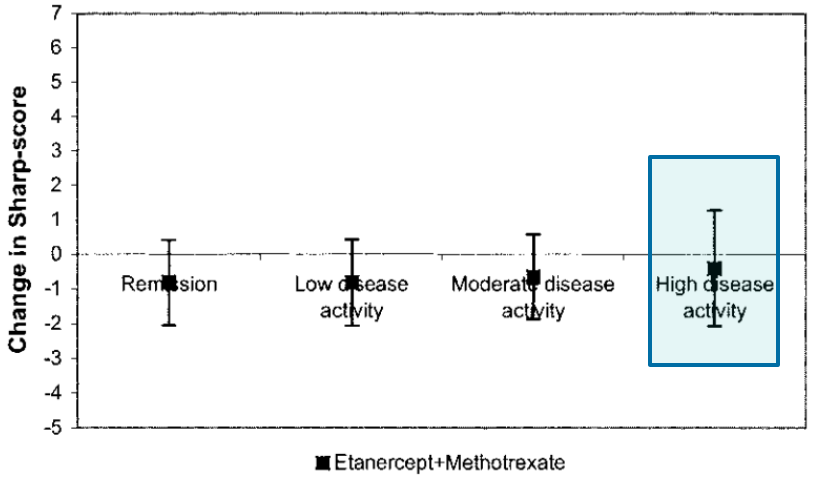
Robert Landewé,[1] Désirée van der Heijde,[1] Lars Klareskog,[2] Ronald van Vollenhoven,[2] and Saeed Fatenejad[3]

TEMPO
2 yrs





Combination therapy with MTX plus ETA uncouples the relationship between disease activity and radiographic progression in RA patients

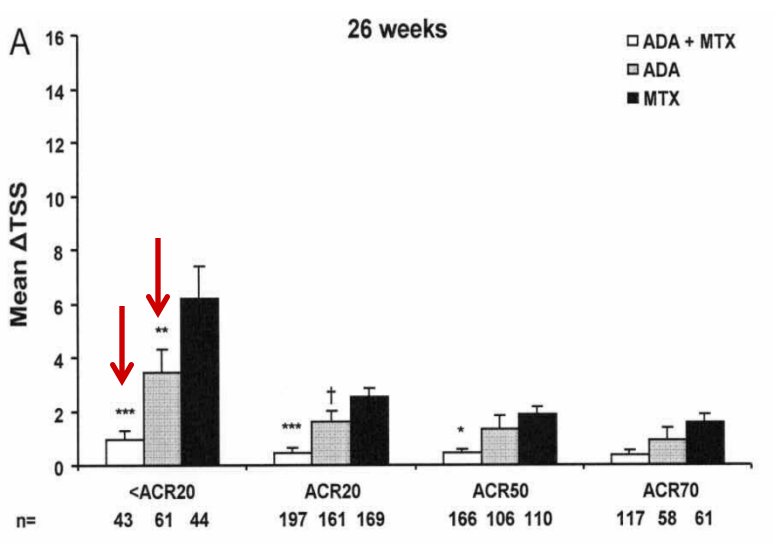


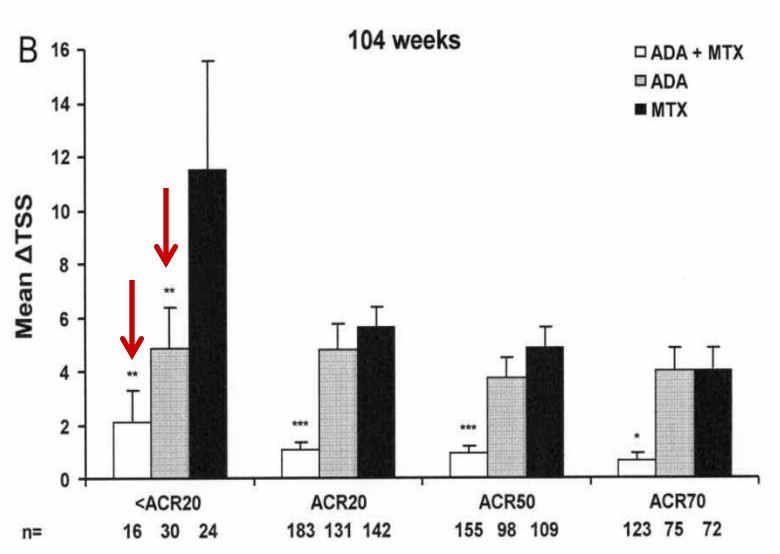
J Rheumatol 2009;36;1429-1441

Less Radiographic Progression with Adalimumab Plus Methotrexate Versus Methotrexate Monotherapy Across the Spectrum of Clinical Response in Early Rheumatoid Arthritis

PAUL EMERY, MARK C. GENOVESE, RONALD van VOLLENHOVEN, JOHN T. SHARP, KAUSHIK PATRA and ERIC H. SASSO

PREMIER
2 yrs



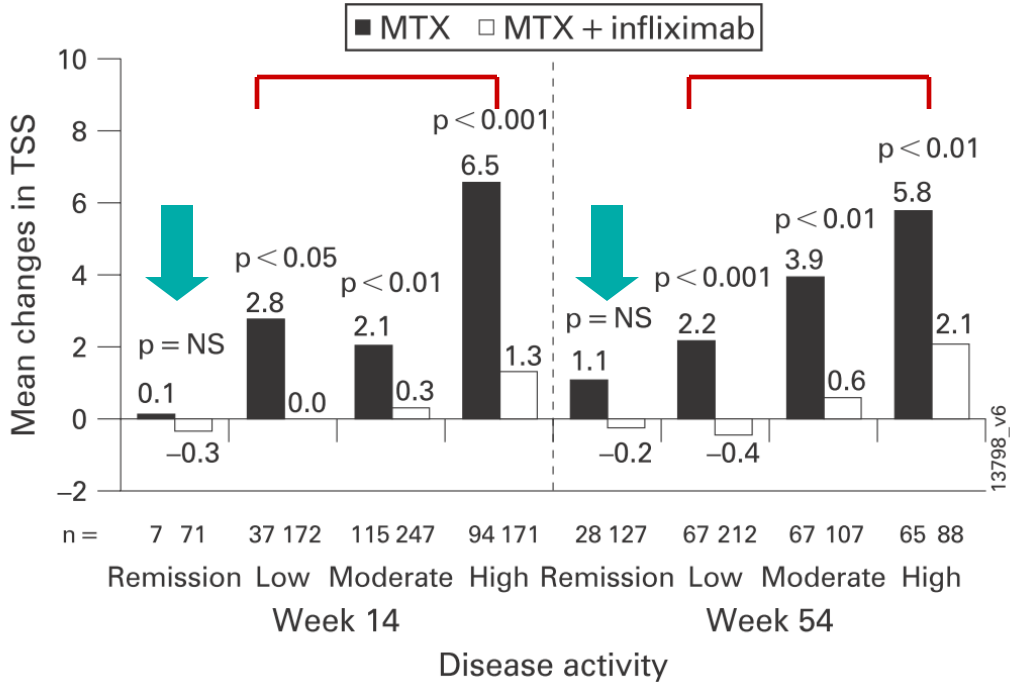


ADA plus MTX controlled radiographic progression better than MTX monotherapy across the spectrum of clinical response or disease activity.

Ann Rheum Dis 2009;**68**:823–827

Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade

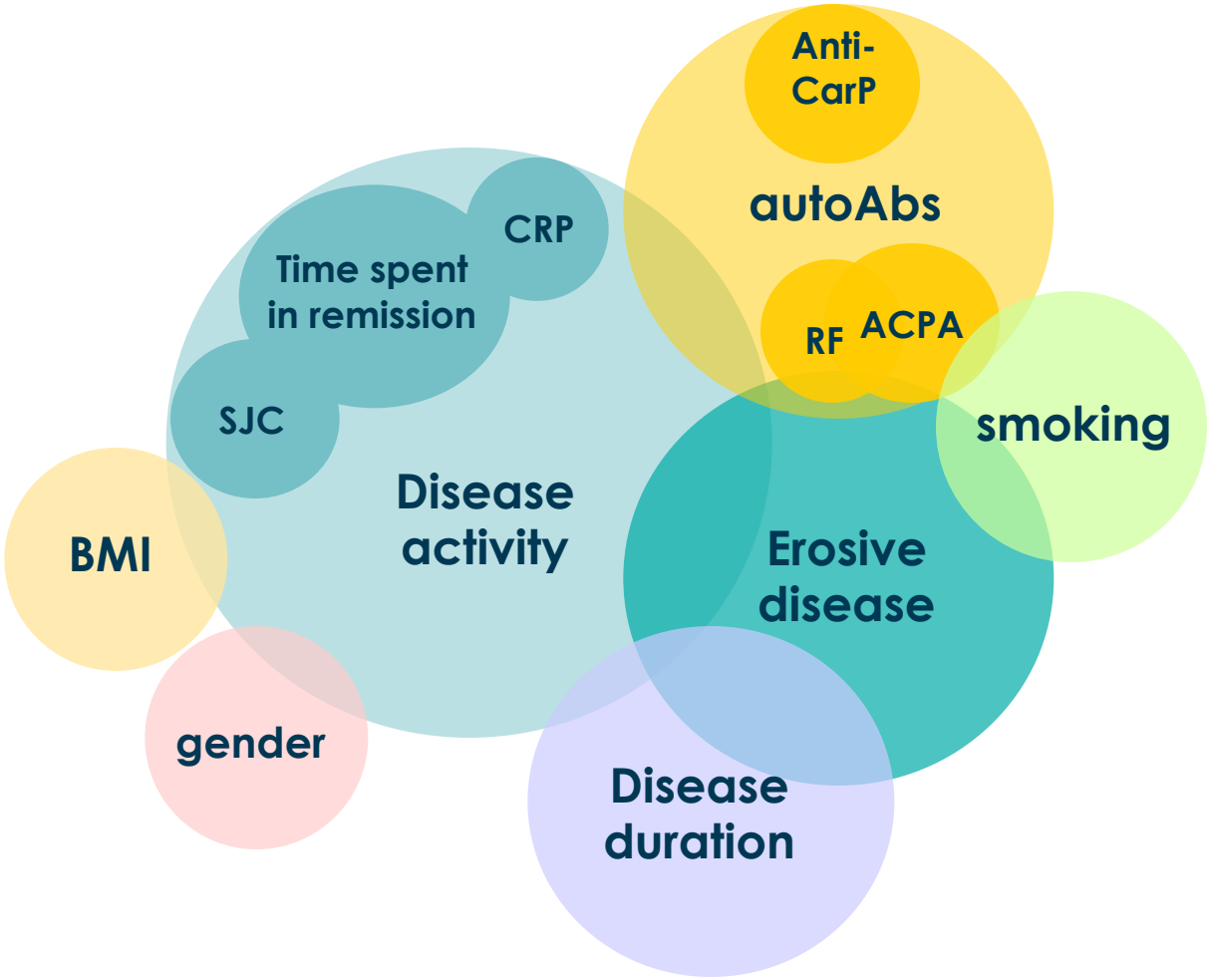
J S Smolen,[1,2] C Han,[11] D M F M van der Heijde,[3] P Emery,[4] J M Bathon,[5] E Keystone,[6] R N Maini,[7] J R Kalden,[8] D Aletaha,[1] D Baker,[10] J Han,[10] M Bala,[11] E W St Clair,[9] for the Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) Study Group



Combination therapy with MTX plus IFX inhibits radiographic progression across all disease activity. In contrast, csDMARD such as MTX can lead to the progression of joint damage, even at low and moderate disease activity levels.

Early achievement of remission with halt the progression in both groups.

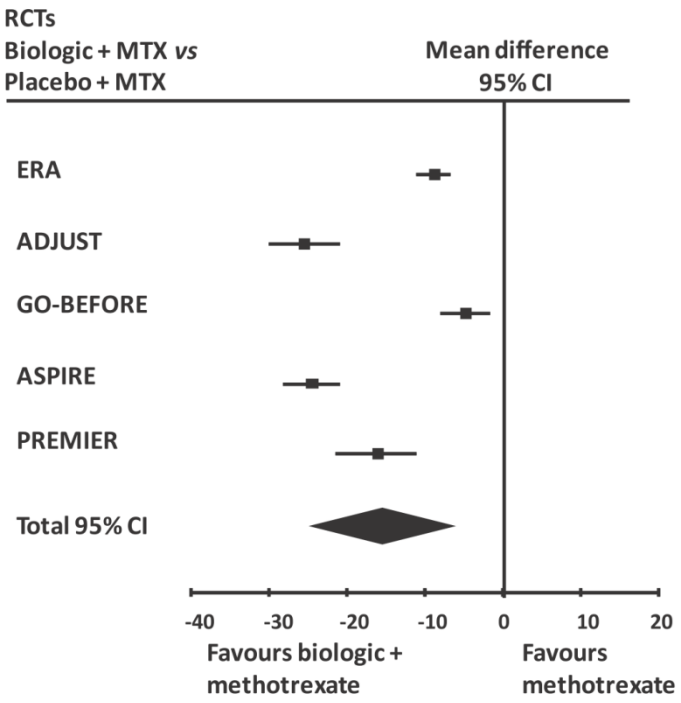
Factor influencing radiographic progression

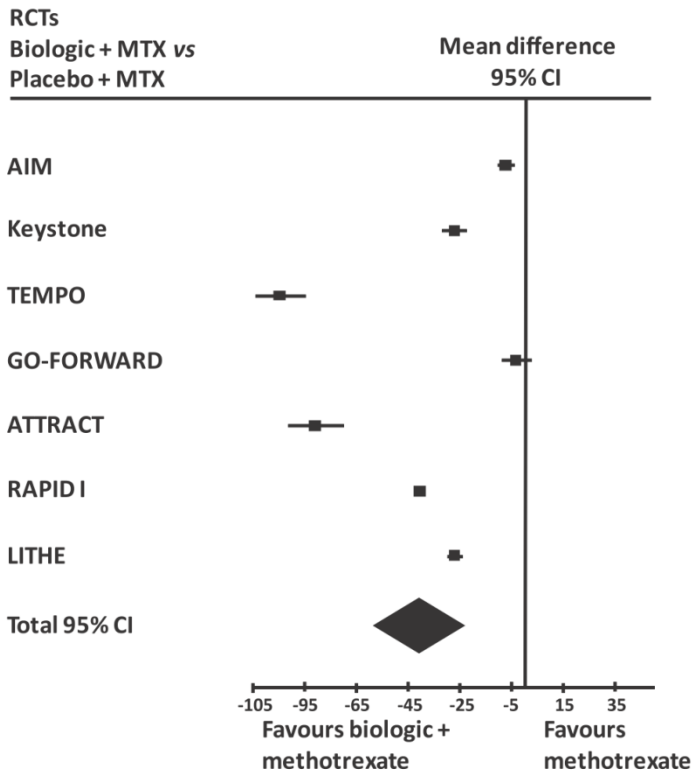


Ther Adv Musculoskel Dis
(2012) 4(4) 213–223

The role of biologic agents in damage progression in rheumatoid arthritis: indirect comparison of data coming from randomized clinical trials

Ennio Giulio Favalli, Francesca Pregnolato, Martina Biggioggero and Pier Luigi Meroni





Baseline score: 2.7-21.9

Standardized annual estimated progression: 2.7-27.35

Baseline score: 23.46-75

Standardized annual estimated progression: 2.4-7.07

All biologics combined with methotrexate are more effective than methotrexate alone in early and long-standing RA patients.

Limitations in comparing radiographic data across RCT

Seminars in Arthritis and Rheumatism 43 (2014) 730–737

The comparison of effects of biologic agents on rheumatoid arthritis damage progression is biased by period of enrolment: Data from a systematic review and meta-analysis

Ennio Giulio Favalli, MD[a,*], Francesca Pregnolato, BSTT[b], Martina Biggioggero, MD[a,c], Pier Luigi Meroni, MD[a,c]

The results of meta-analysis of 14 RCT showed statistically significant differences in slowing/stopping radiographic progression among bDMARDs.

BUT

- 😐 Lack of direct comparison between drugs
- 😐 Different baseline joint damage (progression rate accounts for further joint damage)
- 😐 Study design (IP *vs* PBO or IP *vs* MTX → different baseline characteristic)
- 😐 Prognostic factors for radiographic progression not balanced among different trials
- 😐 Different patterns of radiographic progression
- 😐 Different scoring methods
- 😐 Inter-observer reliability

Inhibition of joint damage: a key target in RA

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- Effect of biological DMARDs on radiographic progression
- **From the historical treatment approach to the *treat to target* strategy**
- A step forward: the comprehensive disease control

RHEUMATOID ARTHRITIS - CLASSIFICATION

Criterion	1987		2010	
Morning stiffness	1	At least 1 hour	NA	
Joint involvement	1	≥ 3 joints	0	1 large joint
			1	2-10 large joints
Arthritis of hand joints	1		2	1-3 small joints (+/- large joints)
			3	4-10 small joints (+/- large joints)
Symmetric arthritis	1	≥ 1swollen joint	5	> 10 (at least 1 small)
Rheumatoid nodules	1		NA	
Serology	1	RF +	0	RF - and ACPA –
			2	RF + or ACPA + (low titer)
			3	RF + or ACPA + (high titer)
Radiographic changes	1	Erosions or unequivocal decalcification in/adjacent to involved joints	NA	
Acute phase reactants	NA		0	Normal CRP and ESR
			1	Abnormal CRP or ESR
Duration of symptoms	NA		0	< 6 weeks
			1	≥ 6 weeks

RA TREATMENT STRATEGIES

Ann Rheum Dis 2010;**69**:631–637

Treating rheumatoid arthritis to target: recommendations of an international task force

Josef S Smolen,[1,2] Daniel Aletaha,[1] Johannes W J Bijlsma,[3] Ferdinand C Breedveld,[4] Dimitrios Boumpas,[5] Gerd Burmester,[6] Bernard Combe,[7] Maurizio Cutolo,[8] Maarten de Wit,[9] Maxime Dougados,[10] Paul Emery,[11] Alan Gibofsky,[12] Juan Jesus Gomez-Reino,[13] Boulos Haraoui,[14] Joachim Kalden,[15] Edward C Keystone,[16] Tore K Kvien,[17] Iain McInnes,[18] Emilio Martin-Mola,[19] Carlomaurizio Montecucco,[20] Monika Schoels,[2] Desirée van der Heijde,[4] for the T2T Expert Committee

10 recommendations on treating rheumatoid arthritis to target based on both evidence and expert opinion:

(1) The primary target for treatment of rheumatoid arthritis should be a state of clinical remission.
(2) Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.
(3) While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease.
(4) Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.
(5) Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission.
(6) The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.
(7) Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.
(8) The desired treatment target should be maintained throughout the remaining course of the disease.
(9) The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of co-morbidities, patient factors and drug-related risks.
(10) The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist.

"x-rays should be obtained annually and potential progression of joint damage be estimated (not scored)"

Level of evidence IV, strength of recommendation D, level of agreement 9.3

Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force

Smolen JS, *et al*. *Ann Rheum Dis* 2016;**75**:3–15.

Ann Rheum Dis 2010;**69**:631–637

Treating rheumatoid arthritis to target: recommendations of an international task force

Josef S Smolen,[1,2] Daniel Aletaha,[1] Johannes W J Bijlsma,[3] Ferdinand C Breedveld,[4] Dimitrios Boumpas,[5] Gerd Burmester,[6] Bernard Combe,[7] Maurizio Cutolo,[8] Maarten de Wit,[9] Maxime Dougados,[10] Paul Emery,[11] Alan Gibofsky,[12] Juan Jesus Gomez-Reino,[13] Boulos Haraoui,[14] Joachim Kalden,[15] Edward C Keystone,[16] Tore K Kvien,[17] Iain McInnes,[18] Emilio Martin-Mola,[19] Carlomaurizio Montecucco,[20] Monika Schoels,[2] Desirée van der Heijde,[4] for the T2T Expert Committee

Final set of 10 recommendations on treating rheumatoid arthritis to target based on both evidence and expert opinion*

2014		2010	
1.	The primary target for treatment of rheumatoid arthritis should be a state of clinical remission	1.	The primary target for treatment of rheumatoid arthritis should be a state of clinical remission
2.	Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity	2.	Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity
3.	While remission should be a clear target, low-disease activity may be an acceptable alternative therapeutic goal, particularly in long-standing disease	3.	While remission should be a clear target, based on available evidence low-disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease
4	The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions	6.	The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions
5	The choice of the (composite) measure of disease activity and the target value should be influenced by comorbidities, patient factors and drug-related risks	9.	The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of comorbidities, patient factors and drug-related risks
6.	Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every six months) for patients in sustained low-disease activity or remission	5.	Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low-disease activity or remission
7.	Structural changes, functional impairment and comorbidity should be considered when making clinical decisions, in addition to assessing composite measures of disease activity	7.	Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity
8.	Until the desired treatment target is reached, drug therapy should be adjusted at least every three months*	4.	Until the desired treatment target is reached, drug therapy should be adjusted at least every three months
9.	The desired treatment target should be maintained throughout the remaining course of the disease	8.	The desired treatment target should be maintained throughout the remaining course of the disease
10.	The rheumatologist should involve the patient in setting the treatment target and the strategy to reach this target	10.	The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist

Level of evidence IV, strength of recommendation D, level of agreement 9.47

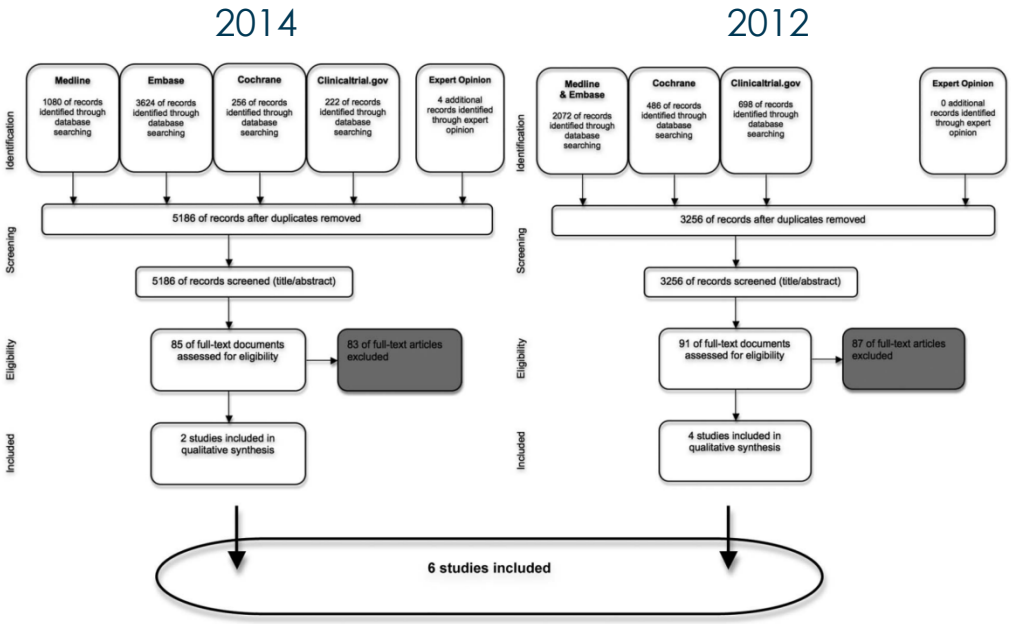
Level of evidence IV, strength of recommendation D, level of agreement 9.3

EXTENDED REPORT

Ann Rheum Dis 2016;**75**:16–22.

Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update

Michaela A Stoffer,[1,2] Monika M Schoels,[3] Josef S Smolen,[1,3] Daniel Aletaha,[1] Ferdinand C Breedveld,[4] Gerd Burmester,[5] Vivian Bykerk,[6] Maxime Dougados,[7] Paul Emery,[8] Boulos Haraoui,[9] Juan Gomez-Reino,[10] Tore K Kvien,[11] Peter Nash,[12] Victoria Navarro-Compán,[4,13] Marieke Scholte-Voshaar,[14] Ronald van Vollenhoven,[15] Désirée van der Heijde,[4] Tanja A Stamm[1]



Study	N°	Outcome	Follow-up (interval)	Radiographic outcome
Goekoop-Ruiterman (Leiden Cohort)	234	DAS remission	3 months	less progression in T2T
ESPOIR/GUEPARD	130 vs 65	DAS28 LDA	Monthly vs 0-24-52	Less progression in T2T group at 12 months
Van Eijk (STREAM)	42 vs 40	X-ray progress.	3 months	Tendency to less progression in more aggressive treatment group at 24 months

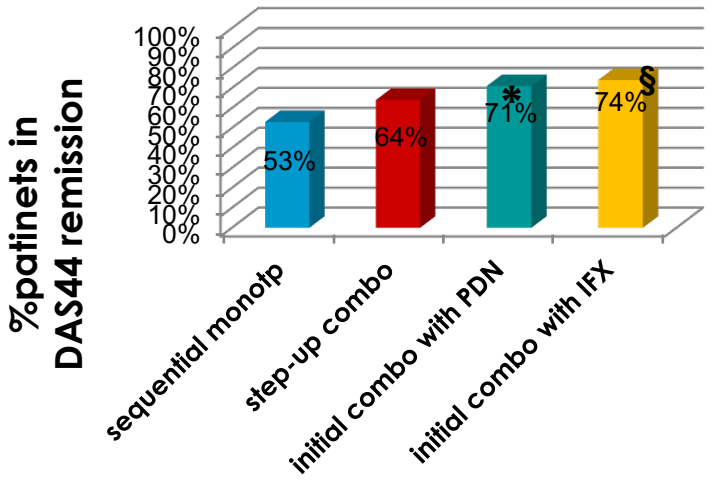
Goekoop-Ruiterman YP et al , Ann Rheum Dis 2010; Soubrier M et al, Ann Rheum Dis 2011; van Eijk IC et al, Rheumatology 2012

Arthritis Rheum. 2005;52:3381-90.

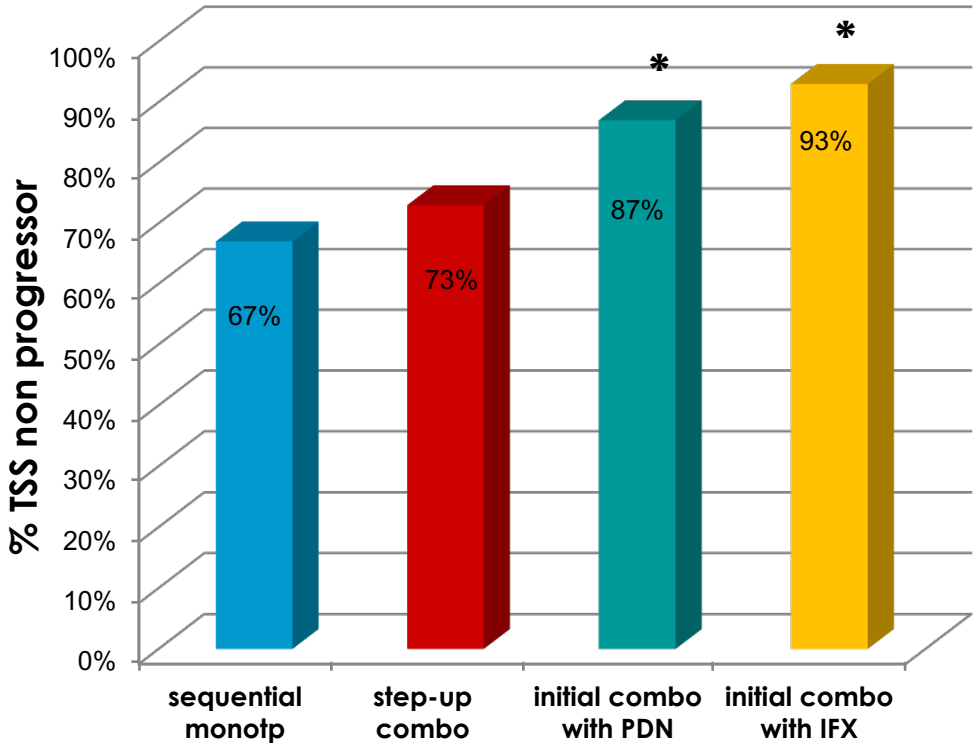
Clinical and Radiographic Outcomes of Four Different Treatment Strategies in Patients With Early Rheumatoid Arthritis (the BeSt Study)

A Randomized, Controlled Trial

Y. P. M. Goekoop-Ruiterman,[1] J. K. de Vries-Bouwstra,[2] C. F. Allaart,[1] D. van Zeben,[3] P. J. S. M. Kerstens,[4] J. M. W. Hazes,[5] A. H. Zwinderman,[6] H. K. Ronday,[7] K. H. Han,[8] M. L. Westedt,[9] A. H. Gerards,[10] J. H. L. M. van Groenendael,[11] W. F. Lems,[12] M. V. van Krugten,[13] F. C. Breedveld,[1] and B. A. C. Dijkmans[14]



*p<0.004 *vs* group 1; § p<0.001 *vs* group 1



*p<0.001 for groups 1 and 2 vs groups 3 and 4

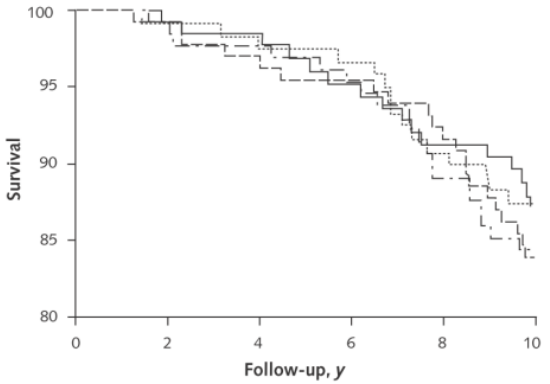
The number of patients without progression of radiographic joint damage after 1 year was higher in groups 3 and 4 than in groups 1 and 2.

Annals of Internal Medicine 2016;164:523-531.

Long-Term Outcomes of Patients With Recent-Onset Rheumatoid Arthritis After 10 Years of Tight Controlled Treatment

A Randomized Trial

Iris M. Markusse, MD, PhD; Gülşah Akdemir, MD; Linda Dirven, PhD; Yvonne P.M. Goekoop-Ruiterman, MD, PhD; Johannes H.L.M. van Groenendael, MD; K. Huub Han, MD; T.H. Esmeralda Molenaar, MD, PhD; Saskia Le Cessie, PhD; Willem F. Lems, MD, PhD; Peter A.H.M. van der Lubbe, MD, PhD; Pit J.S.M. Kerstens, MD, PhD; André J. Peeters, MD, PhD; H. Karel Ronday, MD, PhD; Peter B.J. de Sonnaville, MD; Irene Speyer, MD; Theo Stijnen, PhD; Saskia ten Wolde, MD, PhD; Tom W.J. Huizinga, MD, PhD; and Cornelia F. Allaart, MD, PhD



Patients at risk, *n*						
Sequential monotherapy	126	125	124	119	114	109
Step-up combination therapy	121	119	116	115	108	104
Initial combination with prednisone	133	132	127	124	119	109
Initial combination with infliximab	128	127	125	122	114	107

"After 10 years of targeted treatment, median progression of joint damage (measured as increase in the SHS) in patients who completed follow-up was low: 2.0 (IQR, 0 to 11.0), 2.5 (IQR, 0 to 13.5), 3.0 (IQR, 0.3 to 11.3), and 1.5 (IQR, 0.0 to 6.0) in strategies 1 to 4, respectively.

"Corrected for the SHS at baseline, mean SHS estimates at year 10 were 14.2, 14.1, 14.6, and 8.9 in strategies 1 to 4, respectively".

Ann Rheum Dis 2011;**70**:611–615.

Disease activity score-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis: data from the GUEPARD trial and ESPOIR cohort

M Soubrier,[1] C Lukas,[2] J Sibilia,[3] B Fautrel,[4] F Roux,[5] L Gossec,[6] S Patternotte,[6] M Dougados[6]

ESPOIR
n=130

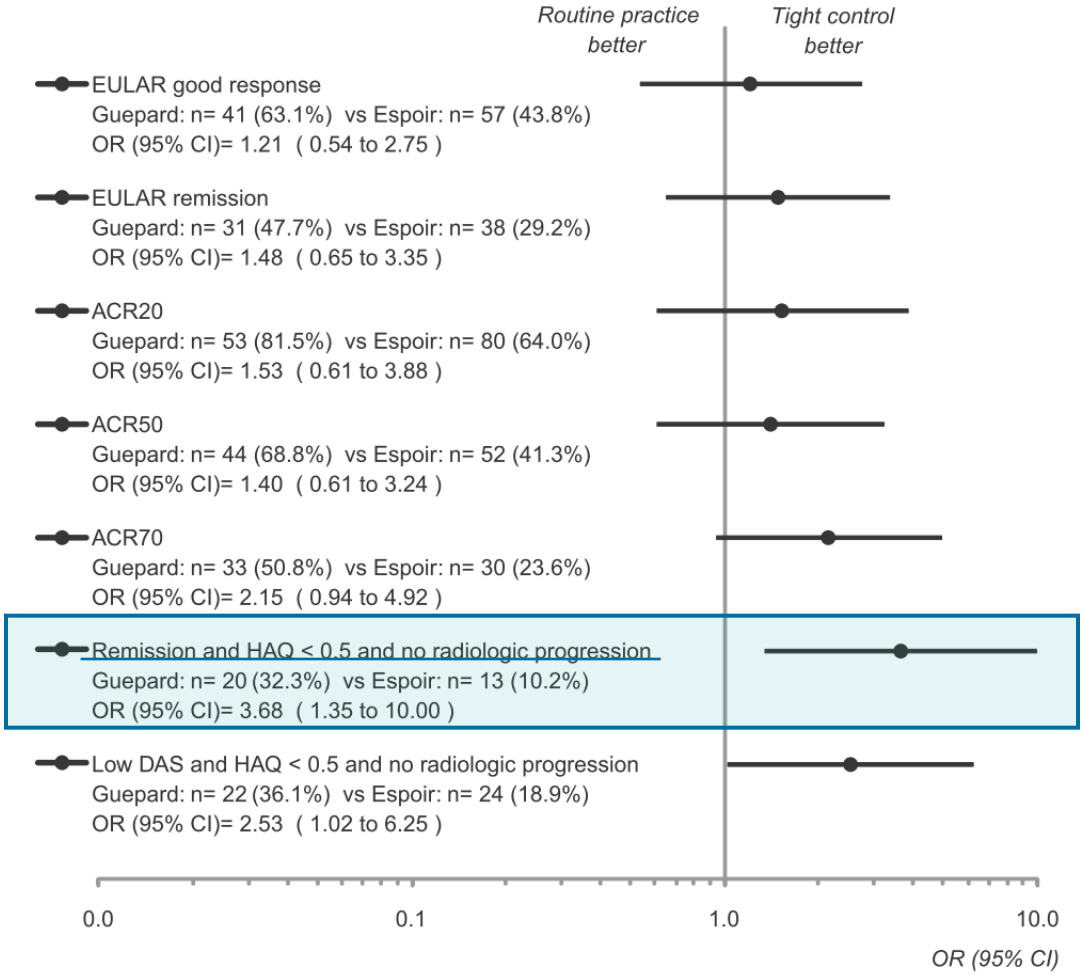
Follow-up
monthly

GUEPARD
n=65

Follow-up
0-24-52 weeks

12-month assessment

decrease in DAS, the number of patients in low DAS or in remission and radiographic progression were similar in the two groups.

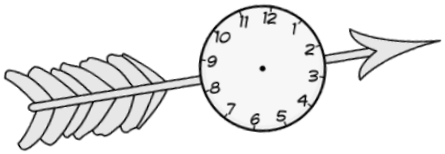


Inhibition of joint damage: a key target in RA

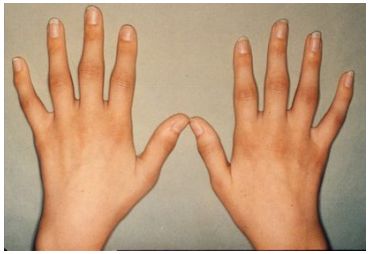
- Rheumatoid Arhtirits: an erosive disease
- Effect of biological DMARDs on radiographic progression
- From the historical treatment approach to the *treat to target* strategy
- **A step forward: the comprehensive disease control**

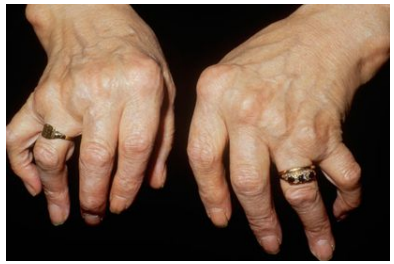
joint damage impacts on quality of life

DISEASE ACTIVITY



JOINT DAMAGE





DISABILITY

reversible → **irreversible**

bone erosions are predictive of a more severe course of disease with a higher degree of disability and increased mortality

RHEUMATOID ARTHRITIS – OUTCOME (pre-bDMARDs)

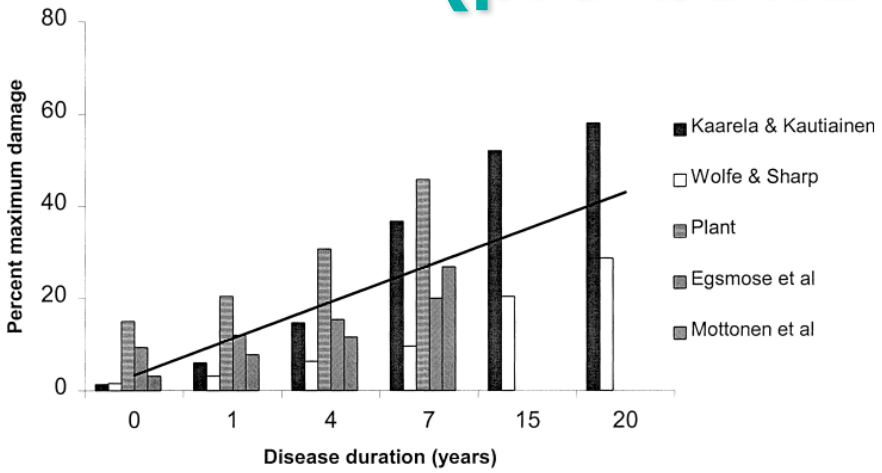


FIG. 1. The increase in joint damage in RA. Based on an amalgamation of data from six studies using Larsen and Sharp scores [15–18, 20]. The average rate of progression, shown by the trendline, was an annual increase of 1.8% of possible maximum damage.

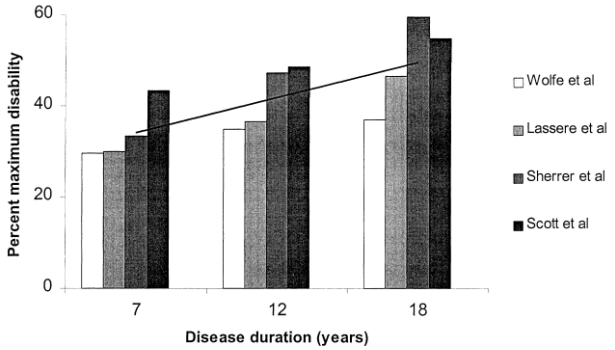


FIG. 2. The increase in disability in RA. Based on an amalgamation of data from four studies [33–35, and additional primary data from Kings College Hospital] using the HAQ to assess disability. The average increase in disability, shown by the trendline, was an annual increase of 1.4% of possible maximum disability.

TABLE 3. Relationship between radiological joint damage and functional disability (assessed by the HAQ) in late RA

Study	Year	Patients	Study type	Disease duration	X-ray damage and function	
					Correlation	Significance
Kaarela and Sarna [52]	1993	103	8 yr follow-up	>8 yr	0.68	$P < 0.001$
Larsen [53]	1988	200	Cross-sectional	Mean 14.6 yr	Not given	$P < 0.01$
Regan-Smith *et al.* [54]	1989	54	Cross-sectional	Mean 8 yr	NS	NS
Pincus *et al.* [11]	1989	259	Cross-sectional	Mean 12.4 yr	0.31	$P < 0.001$
Brühlmann *et al.* [55]	1994	62	Cross-sectional	–	0.39	$P < 0.01$
Hakala *et al.* [56]	1994	103	Cross-sectional	Mean 16.0 yr	0.46	$P < 0.001$
Houssein *et al.* [57]	1997	126	Cross-sectional	Mean 10.5 yr	0.38	$P < 0.001$

Scott DL et al, Rheumatology 2000

ARTHRITIS & RHEUMATISM
Vol. 54, No. 9, September 2006, pp 2784–2792

Measuring Function in Rheumatoid Arthritis

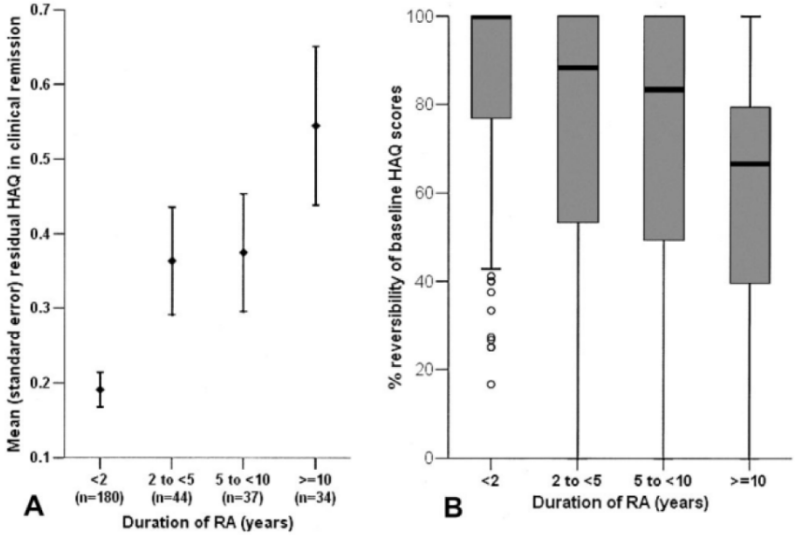
Identifying Reversible and Irreversible Components

Daniel Aletaha,[1] Josef Smolen,[2] and Michael M. Ward[3]

Reversibility is calculated as the relative improvement in baseline HAQ scores at the time of remission (BL HAQ+ Rem HAQx100)

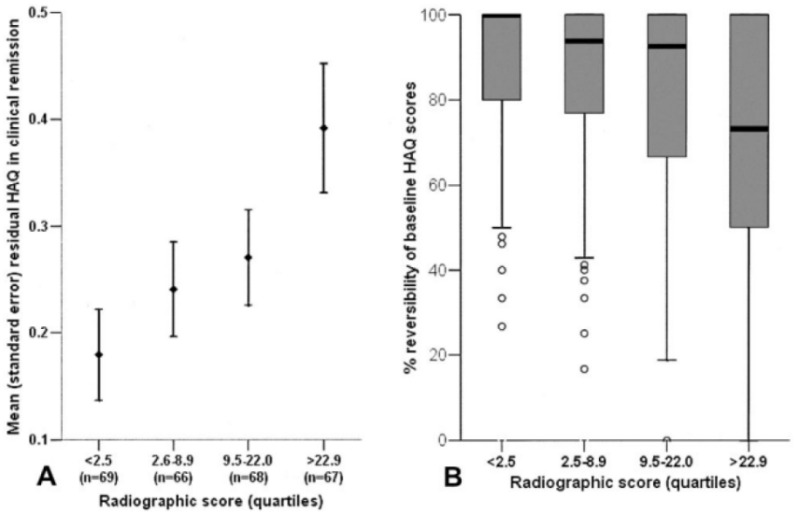
Residual HAQ = HAQ value at the time of remission achievement

N=295



Residual HAQ increases and reversibility decreases according to RA duration

N=270



Residual HAQ increases and reversibility decreases according to radiographic score

COMPREHENSIVE DISEASE CONTROL/REMISSION

Simultaneous achievement of clinical, functional and radiological outcomes

A state achieved by:

3-9% of patients of the MTX+ PBO arms in RCT

10.2-32.3% of patients treated with Adalimumab

23.5% of patients treated with Certolizumab Pegol

16.5% of patients treated with Tocilizumab

Soubrier M et al, 2011; Keystone EC et al Ann Rheum DIs 2013 (ACR abstract), Tanaka Y et al 2014, Burmester G et al 2014, Kubo S et l 2016

EXTENDED REPORT

Comprehensive disease control (CDC): what does achieving CDC mean for patients with rheumatoid arthritis?

Paul Emery,[1] Arthur Kavanaugh,[2] Yanjun Bao,[3] Arijit Ganguli,[3] Parvez Mulani[3]

COMPREHENSIVE DISEASE CONTROL:

1. **CLINICAL** DAS28 <2.6
2. **FUNCTIONAL** HAQ <0.5
3. **STRUCTURAL** Δ mTSS ≤ 0.5

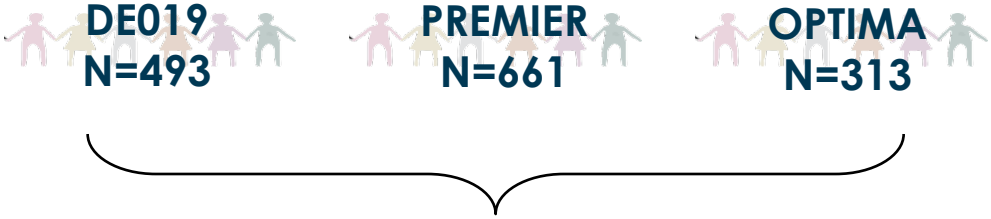
"to quantify the impact of simultaneous achievement of clinical, functional and structural efficacy on work-related outcomes, HRQoL, pain and fatigue (…)"

DE019 **PREMIER** **OPTIMA**

EXTENDED REPORT

Comprehensive disease control (CDC): what does achieving CDC mean for patients with rheumatoid arthritis?

Paul Emery,[1] Arthur Kavanaugh,[2] Yanjun Bao,[3] Arijit Ganguli,[3] Parvez Mulani[3]



1467 patients

at week 26

1267 CDC "non-achievers"

200 CDC "achievers"

Younger age

Lower DAS28(CRP)

Lower HAQ-DI

Lower mTSS

Higher FACIT F

Higher SF-36 (PCS and MCS)

EXTENDED REPORT

Comprehensive disease control (CDC): what does achieving CDC mean for patients with rheumatoid arthritis?

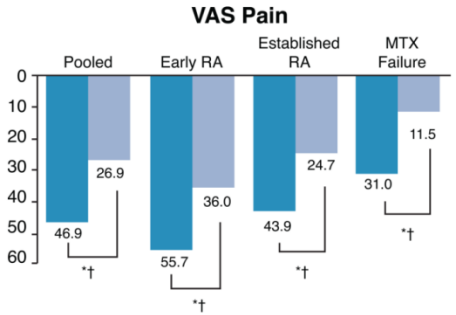
Paul Emery,[1] Arthur Kavanaugh,[2] Yanjun Bao,[3] Arijit Ganguli,[3] Parvez Mulani[3]

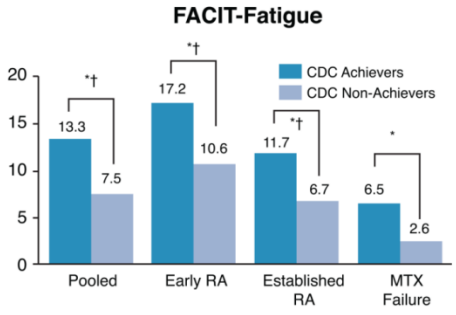
at week 26 and 52

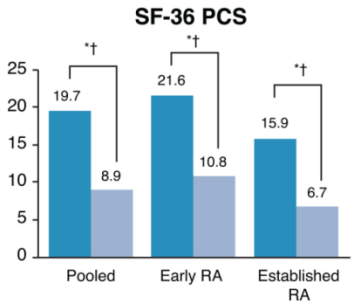
1267 CDC "non-achievers"

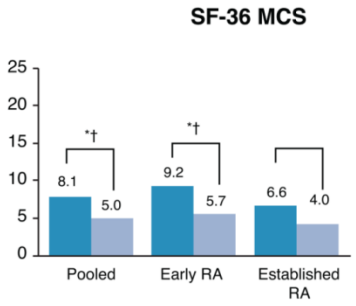
200 CDC "achievers"

week 26

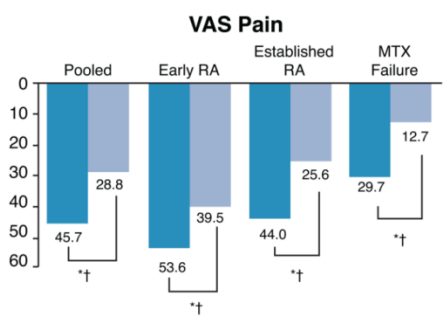


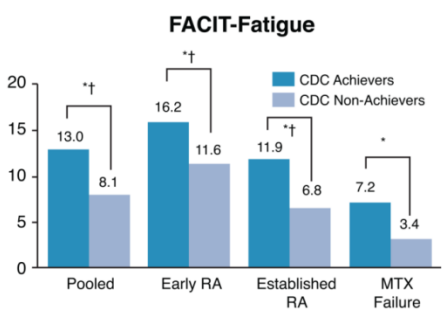


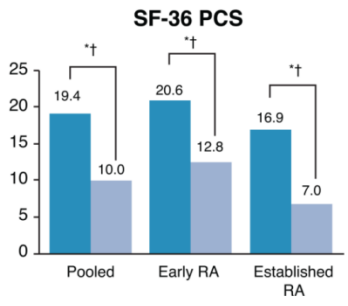


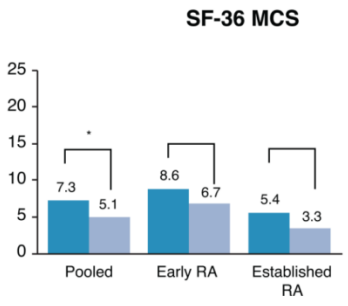


week 52









the differences in SF-36 PCS, VAS-Pain and FACIT-F exceeded their respective MCIDs at week 26 and 52; SF-36 MCS only at week 26.

EXTENDED REPORT

Comprehensive disease control (CDC): what does achieving CDC mean for patients with rheumatoid arthritis?

Paul Emery,[1] Arthur Kavanaugh,[2] Yanjun Bao,[3] Arijit Ganguli,[3] Parvez Mulani[3]

At week 26 and 52 CDC achievement was associated to:

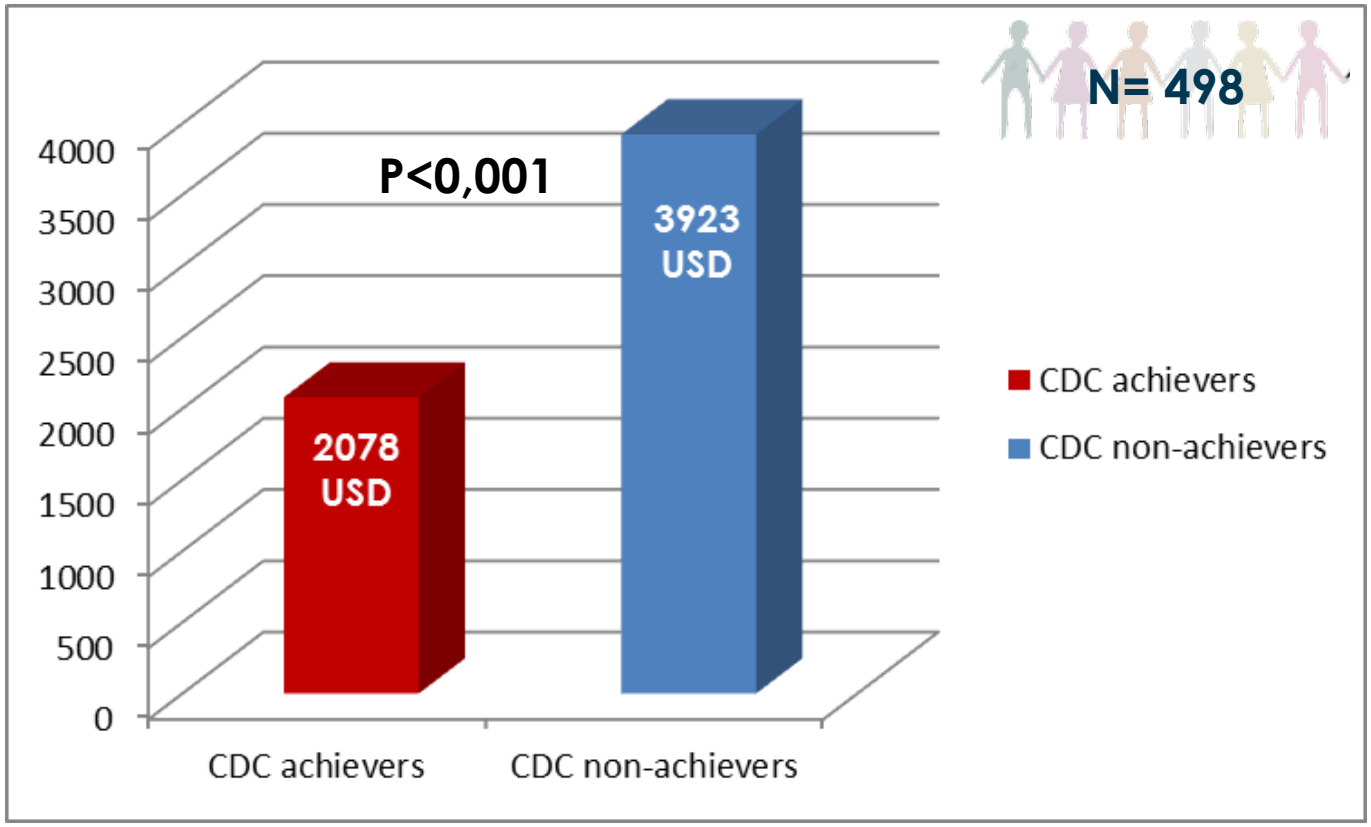
- statistically significant and clinically meaningful difference in VAS-Pain and SF-36 (PCS and MCS) compared to DAS28 remission alone

- statistically significant difference in VAS-Pain and SF-36 (PCS and MCS) compared to achieving normal physical function alone

- statistically significant and clinically meaningful difference in VAS-Pain and SF-36 (PCS and MCS) and FACIT-F compared to no radiographic progression alone

Incremental benefit related to achieving all three components

impact of CDC achievement on direct medical expenditures



Data from the 2011 Medical Expenditure Panel Survey (MEPS) Household Component, and the PREMIER and DE-019 randomized controlled trials.

Emery P et al, Ann Rheum Dis 2015 (ACR abstract)

conclusive remarks

«the times, they are a-changin'» *(Bob Dylan, 2016 Nobel prize for literature)*

"While remission could be the target for adjusting therapy, the goal of every treatment should be inhibition of structural damage and normalise function"

(Emery P et al, Ann Rheum Dis 2015)

WHAT	WHO	WHEN	HOW	WHY
Inhibition of joint damage progression	**All RA patients**	**The earlier, the better**	**T2T strategy tight control CDC**	**↓ disability and ↑ QoL**

Inhibition of joint damage: a key target in RA

Acknowledgement

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Francesca Miranda

Carlo Perricone

Simona Truglia

Genova, 21.10.2016

SAPIENZA
UNIVERSITÀ DI ROMA

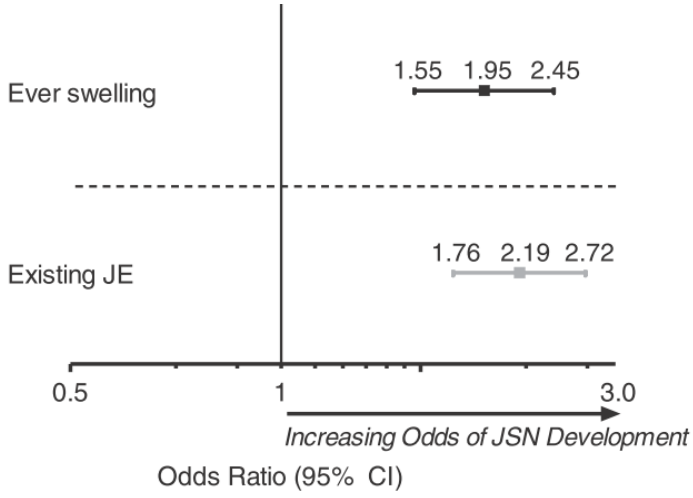
OSTEO RHEUMATOLOGY 2016

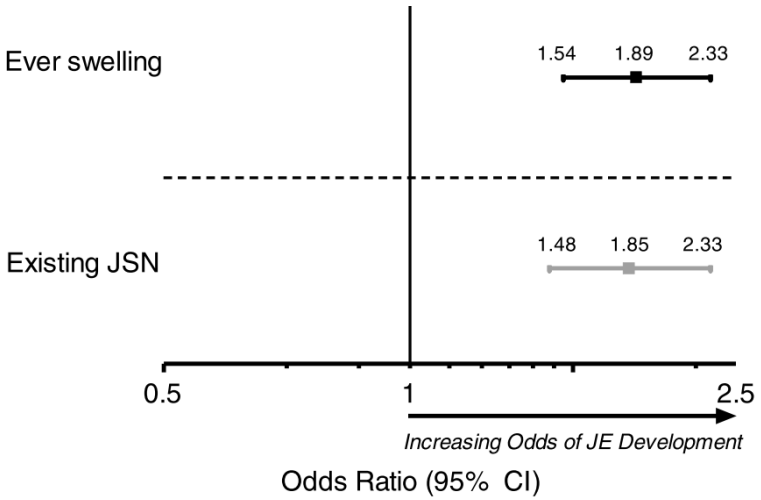
RHEUMATOID ARTHRITIS – OUTCOME

Arthritis Research & Therapy (2015) 17:133

Existing joint erosions increase the risk of joint space narrowing independently of clinical synovitis in patients with early rheumatoid arthritis

Robert Landewé[1*], Josef S Smolen[2], Stefan Florentinus[3], Su Chen[4], Benoît Guérette[4] and Désirée van der Heijde[5]





existing joint erosion or joint space narrowing leads to more erosions and narrowing; at the joint level, existing erosion may also lead to joint space narrowing onset (and vice versa) in joints with no clinical synovitis.

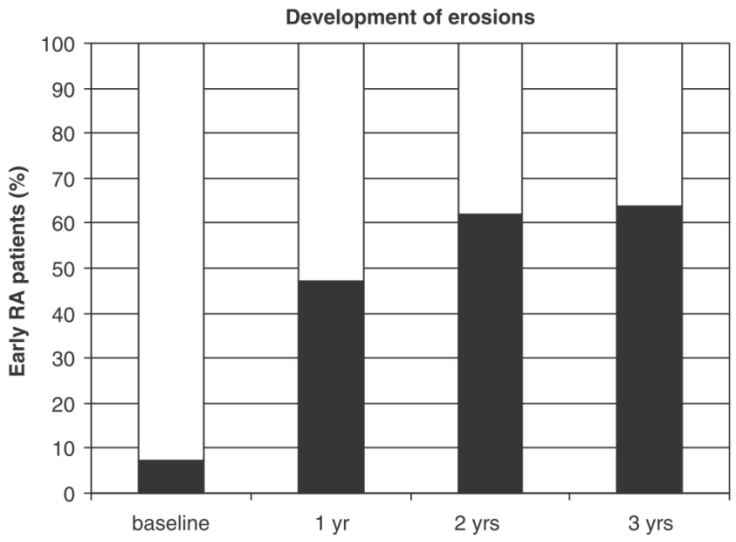
joint damage produces more joint damage

RHEUMATOID ARTHRITIS – OUTCOME

Rheumatology 2007;46:342–349

Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease

K. P. Machold[1], T. A. Stamm[1], V. P. K. Nell[1], S. Pflugbeil[2], D. Aletaha[3], G. Steiner[1], M. Uffmann[4] and J. S. Smolen[1,2]



	Beta	Adjusted R^2	Change in R^2	P
Block 1:		**0.316**	**0.342**	**<0.0001**
RF	*0.321*			*0.050*
Anti-CCP	*0.314*			*0.055*
Block 2:		**0.609**	**0.305**	**<0.0001**
Time in DAS28<3.2	*−0.387*			*<0.0001*
Cumulative swollen joint count	*0.264*			*0.012*
Cumulative CRP	*0.187*			*0.048*

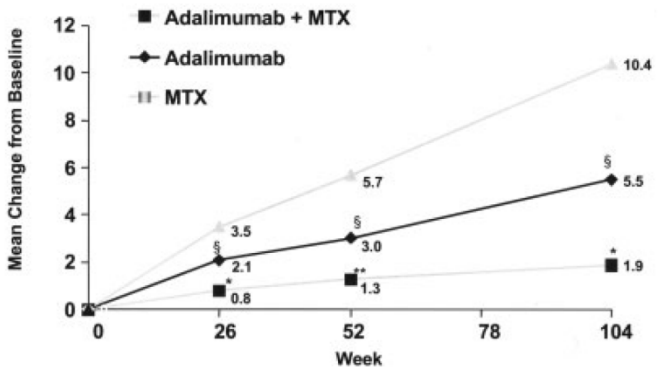
RF and anti-CCP determined 31.6% of the observed change in Larsen scores.

An additional 30.5% can be attributed to the influence of the other three parameters : cumulative CRP,
cumulative swollen joint count and total time in low disease activity and/or remission.

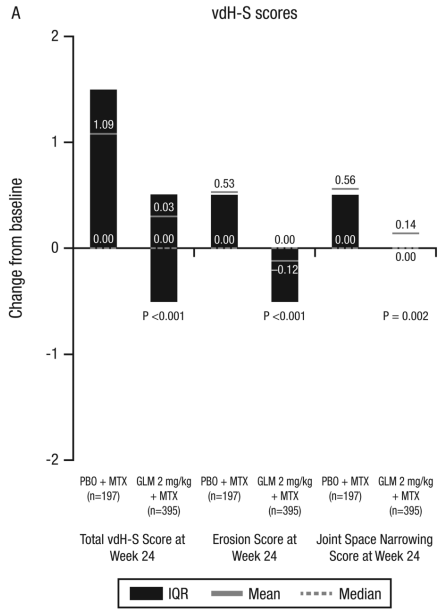
autoAbs and inflammation contribute to joint damage

TNFi -combination therapy over MTX

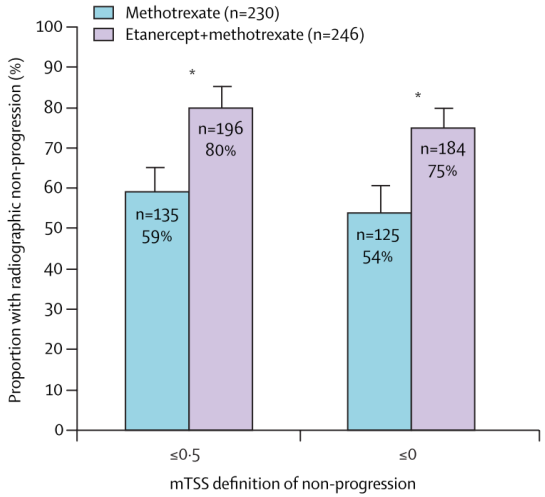
PREMIER (Ada) n=799



GO-FURTHER (Glm) n=592



COMET (Eta) n=476

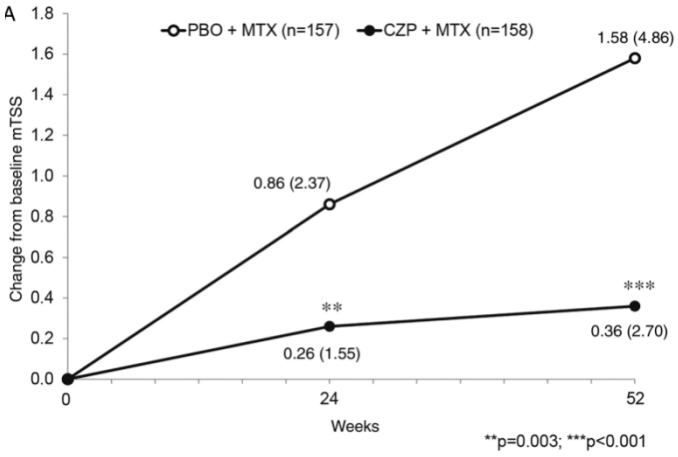


ASPIRE (Ifx) n=1049

Table 2. Change in radiographic scores*

	MTX + placebo (n = 282)	MTX + 3 mg/kg infliximab (n = 359)
Change in van der Heijde modification of the total Sharp score from baseline to week 54†		
Mean ± SD	3.7 ± 9.6	0.4 ± 5.8
Median (IQR)	0.43 (0.0, 4.5)	0.0 (−0.8, 1.3)
P‡		<0.001
Change in erosion score from baseline to week 54§		
Mean ± SD	3.0 ± 7.8	0.3 ± 4.9
Median (IQR)	0.3 (0.0, 3.8)	0.0 (−0.8, 1.3)
P‡		<0.001
Change in JSN score from baseline to week 54§		
Mean ± SD	0.6 ± 2.1	0.1 ± 1.6
Median (IQR)	0.0 (0.0, 0.4)	0.0 (0.0, 0.0)
P‡		<0.001

C-OPERA (Czp) n=315



Breedveld FC t al 2006, van der Hejide D et al 2006, St Clarie et al 2004; Weinbltt EC et l 2013 Atsumi T et al 2016